Official Title of Study:

A Phase 2, Randomized, Double-blind, Placebo-controlled Evaluation of the Safety and Efficacy of BMS-986165 with Background Treatment in Subjects with Lupus Nephritis

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Protocol IM011073

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DOCUMENT HISTORY

Document	Date of Issue	Approvers	Summary of Changes
Original Global Protocol v1.0	14-Nov-2018	[redacted]	Not applicable
Global v2.0_Revised Protocol 1 Global	03-Dec-2018		1. In Section 2.3, preliminary data from Study IM011071 was added. 2. The storage temperature for BMS-986165 was corrected. 3. Section 8.2.1 was updated to be consistent with Table 3.
Global v3.0_Revised Protocol 2 Global	22-Jan-2019		Clarified endpoints, changed urine specimen type to be used for UPCR at various times, added a second stratification variable, added text regarding calculation of UPCR, [redacted] and other changes listed in Amendment 02 (Summary of Changes)
Global Protocol v3.0_Revised Protocol 3 China	12-Mar-2019		Adapted Global Protocol v3.0 to create Revised Protocol 3 China: 1. [redacted] 2. Clarified that the screening DAT will be performed at a local laboratory 3. Added exclusion criterion 3m regarding herbal supplements or traditional Chinese medicines 4. Clarifying language was added to Section 8.7 5. Section 8.7.3 was deleted 6. In Appendix 2, roles specific to investigators in China were noted.

Document	Date of Issue	Approvers	Summary of Changes
Global Protocol v3.0_Revised Protocol 4 Germany	03-Jun-2019	[redacted]	Adapted Global Protocol v3.0 to create Revised Protocol 4 Germany: 1. Consistent with the SmPC for MMF, a pregnancy test was added 8 to 10 days before Visit A1 for WOCBP who will be starting MMF therapy in Part A, and subjects must not donate blood for at least 6 weeks after the final dose of MMF 2. A subject status evaluation at Week 24 was added 3. The unit for MPA concentration was corrected from ng/mL to µg/mL 4. Several sections were amended to clarify that all study treatment will be stopped immediately if a subject becomes pregnant
Global Protocol v3.0_Revised Protocol 5 Italy	10-Jul-2019	[redacted]	Adapted Global Protocol v3.0 to create Revised Protocol 5 Italy: Added serum lipase and amylase to screening and routine laboratory assessments.
Global v4.0_Revised Protocol 6 Global	20-Sep-2019	[redacted]	1. Corrected the units for MPA concentration 2. Modified Table 1 to include enrollment, timing of beginning of the screening period, and SLICC classification 3. Modified several inclusion and exclusion criteria 4. Allowed for rescreening more than once with medical monitor approval 5. Clarified that corticosteroid tapering will be the same for all subjects 6. Emphasized that all treatment medications must be stopped

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			immediately in the case of pregnancy 7. Updated Appendix 7 8. Clarified that subjects may begin treatment with non-study-supplied MMF during the screening period
Global v4.0_Revised Protocol 7 China	11-Oct-2019	[redacted]	Same as for Global Protocol v4.0_Revised Protocol 6 Global
Global v4.0_Revised Protocol 8 Germany	14-Oct-2019		1. Modified Table 1 to include enrollment, timing of beginning of the screening period, and SLICC classification 2. Modified several inclusion and exclusion criteria 3. Allowed for rescreening more than once with medical monitor approval 4. Clarified that corticosteroid tapering will be the same for all subjects 5. Emphasized that all treatment medications must be stopped immediately in the case of pregnancy 6. Updated Appendix 7 7. Clarified that subjects may begin treatment with non-study-supplied MMF during the screening period
Global v4.0_Revised Protocol 9 Italy	14-Oct-2019	[redacted]	1. Corrected the units for MPA concentration 2. Modified Table 1 to include enrollment, timing of beginning of the screening period, and SLICC classification 3. Modified several inclusion and exclusion criteria 4. Allowed for rescreening more than once with medical monitor approval

Document	Date of Issue	Approvers	Summary of Changes
			5. Clarified that corticosteroid tapering will be the same for all subjects 6. Emphasized that all treatment medications must be stopped immediately in the case of pregnancy 7. Updated Appendix 7 8. Clarified that subjects may begin treatment with non-study-supplied MMF during the screening period
Revised Protocol 04 (Global v5.0_Revised Protocol 10 Global[a]) (im011073-revprot04)	06-Aug-2020	[redacted]	1. [redacted] 2. Modified study objectives and endpoints, including new primary and secondary efficacy endpoints 3. Updated UPCR requirements at screening 4. Modified assessments and procedures, including biopsy requirements, prior MMF treatment allowed at screening, and MMF requirements during study 5. Modified inclusion/ exclusion criteria with details regarding the prescreening biopsy, prior MMF treatment, dialysis, current administration of immunosuppressants, and TB screening results 6. [redacted] 7. Modified previous and concomitant therapy allowed and prohibited during the study 8. Clarified requirements for TB screening for subjects who test indeterminate for TB at screening

Document	Date of Issue	Approvers	Summary of Changes
			9. [redacted]

[a] Document naming conventions have been updated. Legacy [redacted] numbering is provided for consistency.

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[redacted]

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1 PROTOCOL SUMMARY

1.1 Synopsis

The primary objectives of this study are to evaluate the safety and efficacy of BMS-986165 compared with placebo with regard to measures of renal function in subjects with lupus nephritis (LN).

Prospective subjects may be enrolled if they meet all eligibility criteria including biopsy results that confirm active LN International Society of Nephrology/Renal Pathology Society (ISN/RPS)[1] Class III or IV (alone or in combination with Class V).

After at least 12 weeks (but ≤ 24 weeks) of treatment with mycophenolate mofetil (MMF) at a dose of 1.5 to 3.0 g/day, subjects with an inadequate renal response may be randomized in a double-blind manner to one of the BMS-986165 treatment groups or placebo as add-on treatment to MMF and corticosteroids. Subjects will be monitored and evaluated every 4 weeks for 52 weeks while they receive blinded study treatment plus continued MMF. Subjects who do not qualify for randomization may continue taking open-label MMF in Part B. [redacted]

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Evaluation of the Safety and Efficacy of BMS-986165 with Background Treatment in Subjects with Lupus Nephritis

Study Phase: 2

Rationale: Lupus nephritis is one of the most serious manifestations of systemic lupus erythematosus (SLE) but the prognosis for patients with LN has not substantially improved since the 1980s.[2] BMS-986165 is a novel, oral, selective tyrosine kinase 2 (TYK2) inhibitor with a unique mechanism of action distinct from other kinase inhibitors that has shown efficacy in subjects with autoimmune diseases and in murine models of SLE and LN.[3, 4, 5] This study is designed to assess whether add-on therapy with BMS-986165 might improve renal function in subjects who do not adequately respond to initial treatment with MMF.

Study Population:

Individuals aged 18 (or local age of majority) to 75 years inclusive who meet all the inclusion criteria and none of the exclusion criteria may be eligible to enroll in the study. Key inclusion criteria include the following:

- Meet the SLE International Collaborating Clinics criteria for SLE

- ISN/RPS Class III or IV (or Class V in combination with Class III or IV) lupus nephritis
- Urine protein:creatinine ratio (UPCR) ≥ 1.5 mg/mg assessed in a 24-hour urine sample for subjects who have had a biopsy within 6 months of screening
- UPCR ≥ 1 mg/mg assessed in a 24-hour urine sample for subjects who have had a biopsy within 3 months of screening

Individuals with any of the following key exclusion criteria will not be eligible to participate: pure ISN/RPS Class V membranous LN; an estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease [MDRD] equation) ≤ 30 mL/minute/1.73 m^2; end-stage renal disease, body mass index ≥ 40 kg/m^2; active infection, or certain other serious illnesses.

See the full protocol for a complete list of inclusion and exclusion criteria.

Primary and Secondary Objectives and Endpoints:

Objective	Endpoint
Primary – 52-week Blinded Treatment Period (Part B)	
• Safety: To assess the safety and tolerability of BMS-986165 in LN	• AEs, vital signs, ECGs, and laboratory abnormalities from baseline through Week 52
• Efficacy: To evaluate the efficacy of BMS-986165 compared with placebo with regard to proteinuria	• Percentage change from baseline in 24-hour UPCR at Week 24
Secondary– 52-week Blinded Treatment Period (Part B)	
• Efficacy – To evaluate the efficacy of BMS-986165 with regard to measures of renal function and SLE activity	• PRR at Week 24, defined as ≥ 50% reduction from baseline in 24-hour UPCR • CRR at Week 24, defined as both of the following: – 24-hour UPCR ≤ 0.5 mg/mg – eGFR ≥ 60 mL/min or ≤ 20% decrease from baseline • CRR at Week 52 • CRR + successful CS taper to ≤ 7.5 mg/day at Week 24 • CRR + successful CS taper to ≤ 7.5 mg/day at Week 52 • PRR at Week 52

AE = adverse event; CRR = complete renal response; CS = corticosteroid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; PRR = partial renal response; SLE = systemic lupus erythematosus; UPCR = urine protein:creatinine ratio

Note: eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation

Overall Design:

This is a 3-part, multicenter, randomized, double-blind study in which eligible subjects will be assessed for renal response after having received a total of at least 12 weeks (but ≤ 24 weeks) of treatment with MMF at a target dose of 1.5 to 3.0 g/day. Subjects will receive 12 weeks of target-dose MMF in Part A of the study if they have not been taking target-dose MMF at screening.

Subjects who have been taking target-dose MMF for ≥ 1 day but < 12 weeks at screening will continue to receive target-dose MMF in Part A until they reach 12 weeks of total MMF treatment. Subjects who have been taking target-dose MMF for ≥ 12 weeks but ≤ 24 weeks at screening will enter the study at Visit A4 to immediately be assessed for renal response and entry into Part B.

Subjects with an inadequate renal response to MMF may be randomized to blinded study treatment with one of two doses of BMS-986165 or placebo as add-on therapy to MMF in Part B. Inadequate response is defined as < 50% reduction in 24-hour UPCR from the pre-MMF value and a 24-hour UPCR ≥ 1.0 mg/mg. Randomized subjects will continue taking open-label MMF with or without corticosteroids. Randomization will be stratified by baseline UPCR < 3.0 mg/mg versus ≥ 3.0 mg/mg and the total cumulative intravenous (IV) corticosteroid (methylprednisolone or parenteral equivalent) dose given in the 16 weeks before randomization (< 250 mg versus ≥ 250 mg).

Subjects who meet the criteria to continue in Part B but do not meet the randomization criteria may continue in Part B on open-label MMF with or without corticosteroids and will have the same assessments in Part B as randomized subjects. These nonrandomized subjects will exit the study at the end of Part B.

Corticosteroids are permitted but not required in this study. Subjects who are taking corticosteroids will have their dose tapered (if possible) during Part B.

In Part B, all (randomized and nonrandomized) subjects will be evaluated at study visits every 4 weeks through Week 52. [redacted]

Optional renal biopsies may be performed at Week 52 [redacted], as well as at the end of treatment for subjects who discontinue early if discontinuation occurs after Week 24 of Part B. After the last treatment visit (Week 52[redacted] or early discontinuation), subjects will attend a final end-of-study visit at the end of a 28-day follow-up period.

Number of Subjects:

A sufficient number of individuals will be screened so that approximately 78 subjects will be randomized in Part B of the study (52 subjects in the combined BMS-986165 groups and 26 subjects in the placebo group).

Treatment Arms and Duration:

Subjects who are eligible to continue in Part B of the study will continue open-label MMF with or without corticosteroids. Subjects who also meet the randomization criteria will be randomized in a double-blind manner to add-on therapy with one of the following:

- 3 mg BMS-986165 BID
- 6 mg BMS-986165 BID
- Placebo BID

The total duration of participation in the study is up to [redacted] weeks, which includes the following periods:

- Screening period: approximately 28 days
- Treatment period:
    - Part A: Open-label MMF (1.5 to 3.0 g/day) run-in period of up to 12 weeks, depending on duration of treatment with MMF at the time of screening, with study visits as indicated in Table 2
    - Approximately 1 week between the last visit in Part A and the first visit in Part B
    - Part B: Randomization followed by blinded study treatment for 52 weeks plus continued open-label MMF with or without corticosteroids (or just continued open-label MMF with or without corticosteroids for those who are not randomized); all subjects will attend study visits every 4 weeks and undergo assessments as indicated in Table 3
    - [redacted]
- A follow-up period of 28 ± 3 days followed by an end-of-study visit

Study Treatments:

Study Treatments for Protocol IM011073

Product Description/ Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986165 oral tablet	3 mg or 6 mg	IP	Blinded	Blister card containing 64 tablets	Store at 15°to 25°C. Store in original container. Protect from light.
Placebo matching BMS-986165 oral tablet	N/A	IP	Blinded	Blister card containing 64 placebo tablets	Store at 15°to 25°C. Store in original container. Protect from light.
Mycophenolate mofetil	500 mg	IP	Open label	Bottles or blister card of tablets	See storage conditions on the container

IP = investigational product

Statistical Methods:

A sample size of 52 randomized subjects in the combined BMS-986165 treatment groups (26 subjects in the BMS-986165 6 mg BID group and 26 in the BMS-986165 3 mg BID group) and 26 subjects in the placebo group will provide 88% power (at a one-sided significance level of 0.10) [redacted].

The change from baseline in log-transformed 24-hour UPCR at Week 24 will be analyzed using analysis of covariance (ANCOVA) with treatment groups and randomization stratification factors as fixed effects and the log-transformed baseline value as a covariate added in the model. Relative treatment differences on least-square means and corresponding 2-sided 95% CIs in primary endpoint, the percentage change from baseline in 24-hour UPCR at Week 24 on the original scale, will be provided for combined BMS-986165 treatment groups and placebo. Additionally, least-square means and 2-sided CIs will be provided for the relative difference between each BMS-986165 treatment group and placebo will be provided in similar method for the Full Analysis Set (FAS). There will be no adjustment of the Type 1 error rate for multiple comparisons or testing of multiple endpoints.

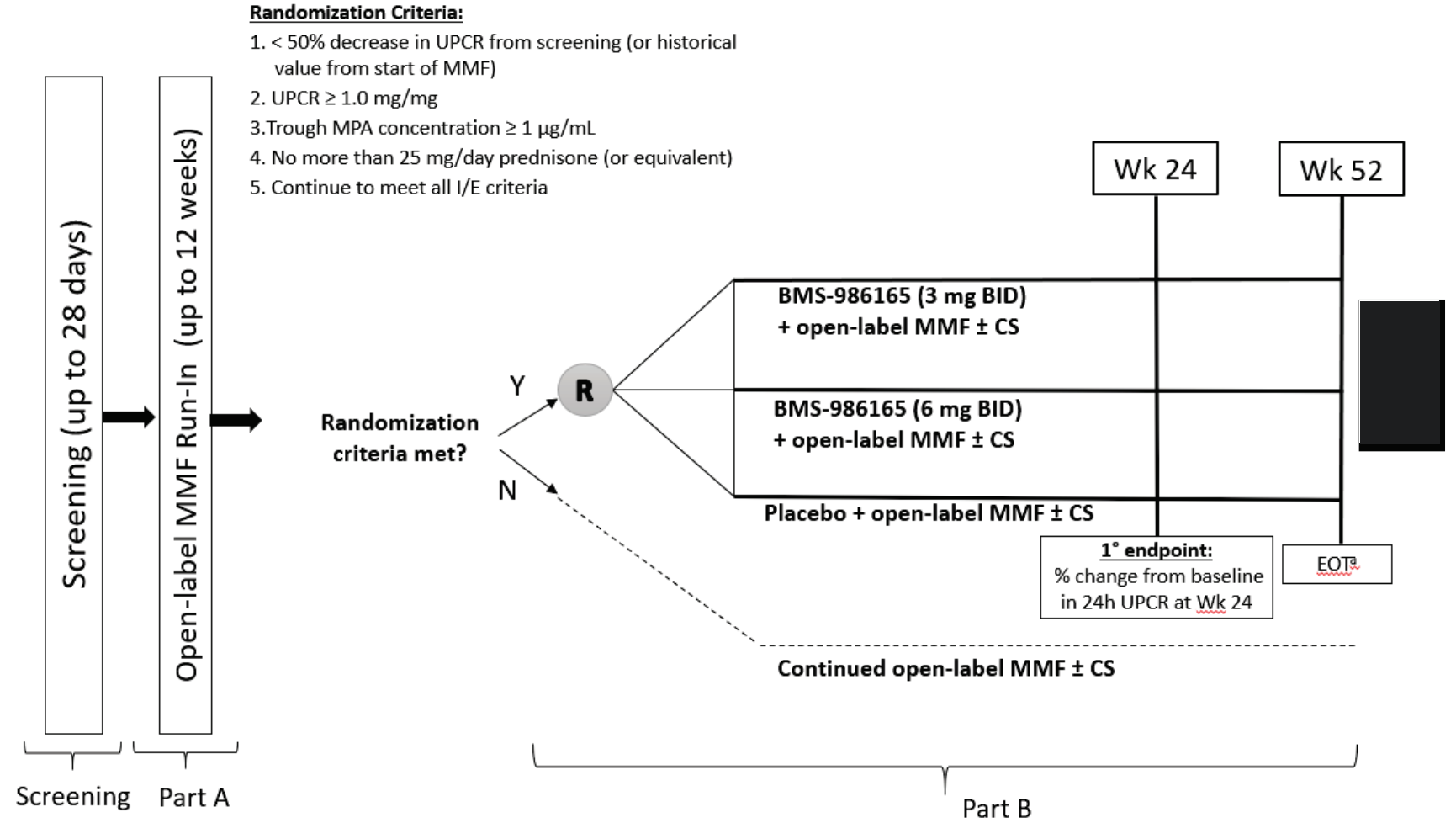
Treatment-emergent adverse events (TEAEs), serious adverse events, deaths, adverse events (AEs) leading to discontinuation of the investigational product (IP), AEs by maximum severity, and AEs by relationship to IP will be summarized by the Medical Dictionary for Regulatory Activities

system organ class and preferred term. All TEAEs, AEs of interest, as well as any adjudicated AE category will also be summarized by preferred term sorted by decreasing frequency.

[redacted] An external Data Monitoring Committee will perform safety monitoring by blinded treatment group.

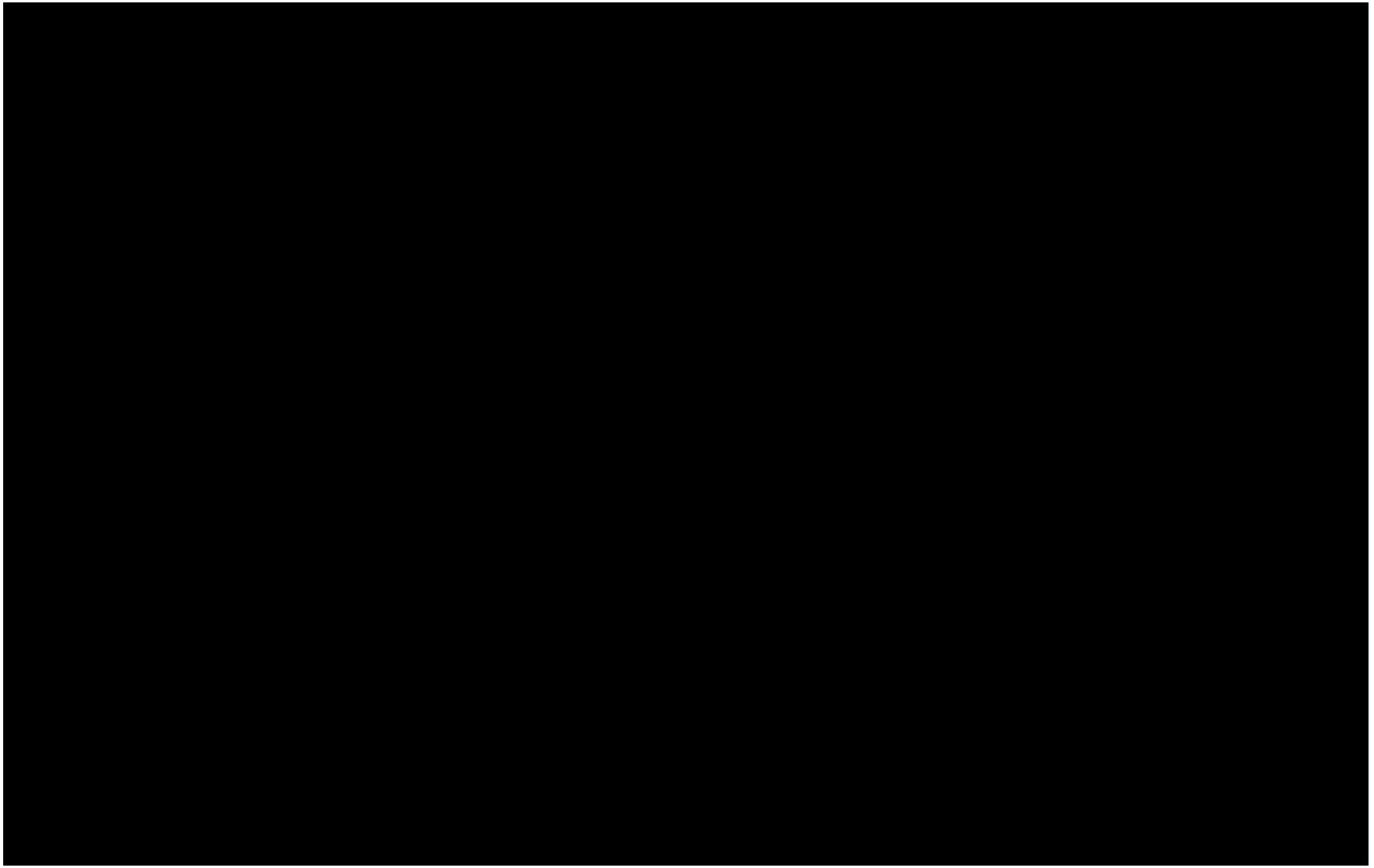
1.2 Schema

The study design schematic for the open-label MMF run-in period (Part A) and the 52-week Blinded Treatment Period (Part B) is presented below.



[redacted]

BID = twice daily; CS = corticosteroid; EOS = end-of-study; EOT = end-of-treatment; d = day; F/U = follow-up; I/E = inclusion/exclusion; [redacted]
MMF = mycophenolate mofetil; MPA = mycophenolic acid; PRR = partial renal response; R = randomization; UPCR = urine protein:creatinine ratio; Wk = week



1.3 Schedules of Activities

Table 1 shows the procedures and assessments to be performed at screening, Table 2 shows these for Part A, Table 3 shows these for Part B [redacted].

Table 1: Screening Procedures and Assessments for Protocol IM011073

Procedure/assessment	Screening (from D-28)	Notes
Informed consent	X	A subject is considered enrolled only when the ICF is signed.
Enroll subject	X	Obtain number from IRT; contact IRT to screen-fail those not eligible
Eligibility assessment	X	
Body weight, height, BMI, vital signs	X	Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes. Blood pressure will be measured twice, at least 5 minutes apart, and the average will be used for the eligibility assessment
Medical history, including SLE and LN history	X	SLE/LN history will include a detailed renal history including laboratory results; information about past and current use of tobacco products should be recorded
SLICC Classification	X	
Complete physical examination	X	
Current/past medications	X	
12-lead ECG	X	
Routine health screening status	X	Investigators will ask subjects whether their routine health screening tests such as bone density testing and cancer screenings (eg, breast and cervical cancer screening for women) are up to date, according to local guidelines. These tests are not required and will not be performed as part of the study.
SAEs	X	SAE collection begins when ICF is signed
Laboratory tests		
Routine chemistry, hematology, and coagulation tests	X	See Protocol Section 8.7.3.1
Trough MPA concentration	X	For subjects already taking MMF at the time of screening; subjects should not have taken MMF for at least 10 hours before sample is collected
hsCRP	X	
Direct antiglobulin test (Coombs test)	X	
Quantitative IgA, IgG, IgM, IgE	X	
Screening serology	X	anti-HBs, HBsAg, anti-HBc, HBV DNA if needed; anti-HCV with HCV RNA if needed; and anti-HIV-1 and anti-HIV-2
[redacted]		
ANA	X	

Table 1: Screening Procedures and Assessments for Protocol IM011073

Procedure/assessment	Screening (from D-28)	Notes
APAs	X	aCl, LA, anti-β2GP1 (IgA, IgG, and IgM)
TSH	X	Free thyroxine will be assessed only if the TSH is abnormal
UA with microscopic examination	X	Clean-catch specimen; if the UA is positive for leukocytes, blood, or bacteria, a urine culture should be performed if appropriate
[redacted]		
UPCR	X	First morning voided specimen (if the first morning void was not collected, the second morning void may be used) Subjects will also collect a 24-hour urine sample for UPCR.
Urine pregnancy test	X	Required for WOCBP only
FSH	X	If needed to confirm postmenopausal status
TB Screening	X	Refer to Section 8.7.2
IGRA assay	X	For TB screening
[redacted]		
Other procedures if all other eligibility criteria are met		
Renal biopsy	X	Documented results within 3 or 6 months before screening may be used, if subject's screening UPCR value is ≥ 1 mg/mg or ≥ 1.5 mg/mg, respectively. Refer to Section 5.1
Chest x-ray (PA and lateral)	X	For TB screening; if available, a documented result of an X-ray or CT scan of the chest within 6 months before screening may be used

aCl = anticardiolipin antibody; ANA = antinuclear antibody; Sm = Smith; APA = antiphospholipid antibody; β2GP1 = beta-2 glycoprotein 1; BMI = body mass index; C = complement; [redacted] CT = computed tomography; D = Day; DNA = deoxyribonucleic acid; [redacted] ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBc = hepatitis B core; HBs = hepatitis B surface; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; ICF = informed consent form; [redacted] Ig = immunoglobulin; IGRA = interferon-gamma release assay; [redacted] IRT = interactive response technology; [redacted] LN = lupus nephritis; MMF = mycophenolate mofetil; MPA = mycophenolic acid; [redacted] PA = posterior-anterior; RNA = ribonucleic acid; [redacted] SAE = serious adverse event; SLE = systemic lupus erythematosus; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; [redacted] TB = tuberculosis; TSH = thyroid-stimulating hormone; UA = urinalysis; UPCR = urine protein:creatinine ratio; US = United States; WOCBP = women of childbearing potential

Table 2: Procedures and Assessments in Part A of Protocol IM011073 (Open-label MMF Run-in Period)

Visit Number	A1	A2	A3	A4[a]	Notes
Week/Day of MMF Treatment[b]	**Day 1**	**Week 4±14d**	**Week 8±14d**	**Week 12±14d**	**Assessments at Visit A4 will be used to determine subjects' eligibility for randomization to IP/placebo or continuation with only open-label MMF/CS in Part B. These assessments will also be used to stratify subjects who are eligible for randomization.**
AEs and SAEs	X	X	X	X	SAE collection begins at the time ICF is signed; AE collection begins at the time of the first MMF dose in Part A; see Section 8.5
Medical history	X				Any medical occurrences after signing the ICF but before the first dose of MMF in Part A will be recorded as medical history. Subjects already on MMF at screening should have medical history recorded at their first visit in Part A.
Body weight and vital signs	X	X	X	X	Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
Concomitant medications	X	X	X	X	
Complete physical examination	X	X	X	X	
Dispense MMF	X	X	X	X	
Baseline indices of disease activity and damage					
[redacted]					
SDI				X	APPENDIX 10
[redacted]					
Laboratory tests					
Routine chemistry and hematology	X	X	X	X	Results from Visit A4 will be the baseline values for Part B
CBC for MMF monitoring	As needed per MMF prescribing information				Weekly during the first month and every 2 weeks for the second and third month of MMF; may be performed at a local laboratory; sites will contact subjects in advance to remind them; see Section 6.2
[redacted]					
ANA				X	

Table 2: Procedures and Assessments in Part A of Protocol IM011073 (Open-label MMF Run-in Period)

Visit Number	A1	A2	A3	A4[a]	Notes
Week/Day of MMF Treatment[b]	**Day 1**	**Week 4±14d**	**Week 8±14d**	**Week 12±14d**	**Assessments at Visit A4 will be used to determine subjects' eligibility for randomization to IP/placebo or continuation with only open-label MMF/CS in Part B. These assessments will also be used to stratify subjects who are eligible for randomization.**
[redacted]					
Trough MPA concentration			X		For randomization assessment; subjects should not have taken MMF for at least 10 hours before sample is collected
[redacted]					
hsCRP				X	
[redacted]					
Serum lipid panel				X	Subjects are required to fast at least 10 hours before sample is collected
APAs				X	LA, aCl, and anti-β2GP1 (IgA, IgG, and IgM)
[redacted]					
TB questionnaire and IGRA assay				X	Only subjects who tested indeterminate for TB at screening must fill out the TB questionnaire and have a repeat IGRA test at Visit A4. Note: Not required for subjects who proceeded straight to Visit A4 after screening (ie, subjects who entered the study with ≥ 12 weeks of MMF treatment). See Section 8.7.2 and APPENDIX 20
[redacted]					

Table 2: Procedures and Assessments in Part A of Protocol IM011073 (Open-label MMF Run-in Period)

Visit Number	A1	A2	A3	A4[a]	Notes
Week/Day of MMF Treatment[b]	**Day 1**	**Week 4±14d**	**Week 8±14d**	**Week 12±14d**	**Assessments at Visit A4 will be used to determine subjects' eligibility for randomization to IP/placebo or continuation with only open-label MMF/CS in Part B. These assessments will also be used to stratify subjects who are eligible for randomization.**
UA with microscopic examination	X	X	X	X	Clean-catch specimen; results from Visit A4 will be the baseline values for Part B; if the UA is positive for leukocytes, blood, or bacteria, a urine culture should be performed if appropriate
UPCR	X	X	X	X	First morning voided specimen; second void may be used if the first morning void was not collected
Urine pregnancy test	X	X	X	X	WOCBP only; Note: subjects beginning MMF in Part A must have an additional test 8 to 10 days after the first dose; may be performed at a local laboratory; sites will contact subjects in advance to remind them
24-hour urine for UPCR [redacted]				X and 7-10 d before	Two 24-hour urine collections are required; one just before Visit A4 and the other approximately 7-10 days before Visit A4. For subjects with ≥ 12 weeks of MMF at the time of screening, Visit A4 and the collection of a single 24-hour specimens should be scheduled promptly (the 24-hour urine from screening will be the first sample)

[redacted] AE = adverse event; ANA = antinuclear antibody; APA = antiphospholipid antibody; C = complement; CBC = complete blood [redacted] hsCRP = high-sensitivity C-reactive protein; ICF = informed consent form; Ig = immunoglobulin; IGRA = interferon-gamma release assay; LA = lupus anticoagulant; MMF = mycophenolate mofetil; MPA = mycophenolic acid; [redacted] SDI= Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; [redacted] TB = tuberculosis; [redacted] UA = urinalysis; UPCR = urine protein:creatinine ratio; US = United States; WOCBP = women of childbearing potential.

[a] Subjects with ≥ 12 weeks (± 3 days) but ≤ 24 weeks of MMF at a dose of 1.5 to 3.0 g/day at screening will enter the study at Visit A4.

[b] Note the ±14-day windows displayed in the table are used to allocate the subject's first Part A visit based on the subject's number of weeks on MMF; the actual visit dates subsequent to the first Part A visit should occur as close to the required timepoint (Week 4, 8 or 12) as possible, with a ±3 day window to complete the visit.

Note: For premenopausal women, study visits and 24-hour urine collections should be scheduled, when possible, for when they are not menstruating.

Note: If the difference in UPCR between the two 24-hour urine specimens is > 20%, a third 24-hour specimen should be collected to determine the average value; the third sample should be collected as soon as possible but no more than 10 days after the first two results are reported.

Note: Not all subjects will attend all visits in Part A, because they will "drop in" at the appropriate time depending on their duration of MMF treatment. Subjects who enter the study having completed ≥ 12 weeks of MMF at a dose of 1.5 to 3.0 g/day will need to complete only Visit A4 after screening.

Table 3: Procedures and Assessments in Part B of IM011073 (52-Week Blinded Treatment Period)

Visit Number	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14/ EOT[a]	B15[a]	Notes
Study Week/Day	D1	W4 D29 ±3d	W8 D57 ±3d	W12 D85 ±3d	W16 D113 ±3d	W20 D141 ±3d	W24 D169 ±3d	W28 D197 ±3d	W32 D225 ±3d	W36 D253 ±3d	W40 D281 ±3d	W44 D309 ±3d	W48 D337 ±3d	W52 D365 ±3d	28-D FU ±3d	The final study visit (for noncontinuing subjects) will occur 28d±3d after the visit at W52
Confirm study eligibility criteria are still met	X															
Evaluate for randomization	X															
Body weight & vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	BP and HR should be measured after the subject has been sitting quietly for at least 5 minutes
Complete physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X	X				X						X	X		
AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.5
Subject Status Evaluation							X									Section 7.2
Indices of disease activity and damage[b]																
rSFI		X	X	X	X	X	X	X	X	X	X	X	X	X		All systems except renal; clinical component only (not treatment) APPENDIX 17
OSS Flare Index		X	X	X	X	X	X	X	X	X	X	X	X	X		APPENDIX 16
[redacted]																

Table 3: Procedures and Assessments in Part B of IM011073 (52-Week Blinded Treatment Period)

Visit Number	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14/ EOT[a]	B15[a]	Notes
Study Week/Day	**D1**	**W4 D29 ±3d**	**W8 D57 ±3d**	**W12 D85 ±3d**	**W16 D113 ±3d**	**W20 D141 ±3d**	**W24 D169 ±3d**	**W28 D197 ±3d**	**W32 D225 ±3d**	**W36 D253 ±3d**	**W40 D281 ±3d**	**W44 D309 ±3d**	**W48 D337 ±3d**	**W52 D365 ±3d**	**28-D FU ±3d**	The final study visit (for noncontinuing subjects) will occur 28d±3d after the visit at W52
Laboratory tests and other procedures																
UA with microscopic examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Clean-catch specimen; if the UA is positive for leukocytes, blood, or bacteria, a urine culture should be performed if appropriate
UPCR		X	X	X	X	X	X	X	X	X	X	X	X	X		First morning voided specimen; second morning void may be used if first morning void was not collected
24-hour urine for UPCR[c]							X and ±7d							X and ±7d		Two 24-hour urine specimens will be collected for Visits B7 and B14; one should be collected at the visit and one returned either before or after per site/ subject preference. The subject must provide both samples within the total 14-day window.
Urine pregnancy test for WOCBP only	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	A negative result within 24 hours before dosing on D1 is required

Table 3: Procedures and Assessments in Part B of IM011073 (52-Week Blinded Treatment Period)

Visit Number	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14/ EOT[a]	B15[a]	Notes
Study Week/Day	**D1**	**W4 D29 ±3d**	**W8 D57 ±3d**	**W12 D85 ±3d**	**W16 D113 ±3d**	**W20 D141 ±3d**	**W24 D169 ±3d**	**W28 D197 ±3d**	**W32 D225 ±3d**	**W36 D253 ±3d**	**W40 D281 ±3d**	**W44 D309 ±3d**	**W48 D337 ±3d**	**W52 D365 ±3d**	**28-D FU ±3d**	The final study visit (for noncontinuing subjects) will occur 28d±3d after the visit at W52
TB questionnaire and IGRA assay							X						X			Only subjects who have indeterminate test results for TB must fill out the TB questionnaire and have a repeat IGRA test. Refer to Section 8.7.2 and APPENDIX 20.
Routine chemistry and hematology		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.7.3.2
Trough MPA concentration							X							X		Subjects should not have taken MMF for at least 10 hours before sample is collected
Serum lipid panel							X							X		Subjects are required to fast at least 10 hours before sample is collected
hsCRP		X	X	X	X	X	X	X	X	X	X	X	X	X		
[redacted]																
ANA							X							X		
[redacted]																
APAs							X							X		LA, aCl, and anti-β2GP1 (IgA, IgG, IgM)

Table 3: Procedures and Assessments in Part B of IM011073 (52-Week Blinded Treatment Period)

Visit Number	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14/ EOT[a]	B15[a]	Notes
Study Week/Day	D1	W4 D29 ±3d	W8 D57 ±3d	W12 D85 ±3d	W16 D113 ±3d	W20 D141 ±3d	W24 D169 ±3d	W28 D197 ±3d	W32 D225 ±3d	W36 D253 ±3d	W40 D281 ±3d	W44 D309 ±3d	W48 D337 ±3d	W52 D365 ±3d	28-D FU ±3d	The final study visit (for noncontinuing subjects) will occur 28d±3d after the visit at W52
[redacted]																

Table 3: Procedures and Assessments in Part B of IM011073 (52-Week Blinded Treatment Period)

Visit Number	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14/ EOT[a]	B15[a]	Notes
Study Week/Day	D1	W4 D29 ±3d	W8 D57 ±3d	W12 D85 ±3d	W16 D113 ±3d	W20 D141 ±3d	W24 D169 ±3d	W28 D197 ±3d	W32 D225 ±3d	W36 D253 ±3d	W40 D281 ±3d	W44 D309 ±3d	W48 D337 ±3d	W52 D365 ±3d	28-D FU ±3d	The final study visit (for noncontinuing subjects) will occur 28d±3d after the visit at W52
[redacted]																
Optional Renal biopsy														X		Within 2 weeks after completion of 52 weeks of study treatment or ET, if ET occurs after Week 2 [redacted]
Clinical drug supplies																
Randomization	X															Subjects who meet all randomization criteria
[redacted]																
MMF issued	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]		All subjects
MMF administration	X----------													----------X		All subjects

Table 3: Procedures and Assessments in Part B of IM011073 (52-Week Blinded Treatment Period)

Visit Number	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14/ EOT[a]	B15[a]	Notes
Study Week/Day	D1	W4 D29 ±3d	W8 D57 ±3d	W12 D85 ±3d	W16 D113 ±3d	W20 D141 ±3d	W24 D169 ±3d	W28 D197 ±3d	W32 D225 ±3d	W36 D253 ±3d	W40 D281 ±3d	W44 D309 ±3d	W48 D337 ±3d	W52 D365 ±3d	28-D FU ±3d	The final study visit (for noncontinuing subjects) will occur 28d±3d after the visit at W52
MMF accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X		All subjects
Blinded study treatment issued	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]		Randomized subjects only
Blinded study treatment administration	X----------													----------X		Randomized subjects only
Blinded study treatment accountability		X	X	X	X	X	X	X	X	X	X	X	X	X		Randomized subjects only
Unused blinded study treatment collected		X	X	X	X	X	X	X	X	X	X	X	X	X		Randomized subjects only

aCl = anticardiolipin antibody; AE = adverse event; ANA antinuclear antibody; APA = antiphospholipid antibody; β2GP1 = beta-2 glycoprotein 1; BP = blood pressure; C = complement; D = day; [redacted] ECG = electrocardiogram; EOT = end of treatment; [redacted] ET = early termination; FU = follow-up (end-of-study visit); HR = heart rate; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IGRA = interferon-gamma release assay; IP = investigational product; IRT = interactive response technology; LA = lupus anticoagulant [redacted] MMF = mycophenolate mofetil; MPA = mycophenolic acid; [redacted] OSS = Ohio SLE Study; [redacted] rSFI = revised Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Flare Index; SAE = serious adverse event; [redacted] TB = tuberculosis; [redacted] UA = urinalysis; UPCR = urine protein:creatinine ratio; US = United States; W = week; WOCBP = women of childbearing potential

[a] Visit B14 is the last treatment visit for subjects who do not continue treatment during the LTE Period. Only these noncontinuing subjects should attend Visit B15.

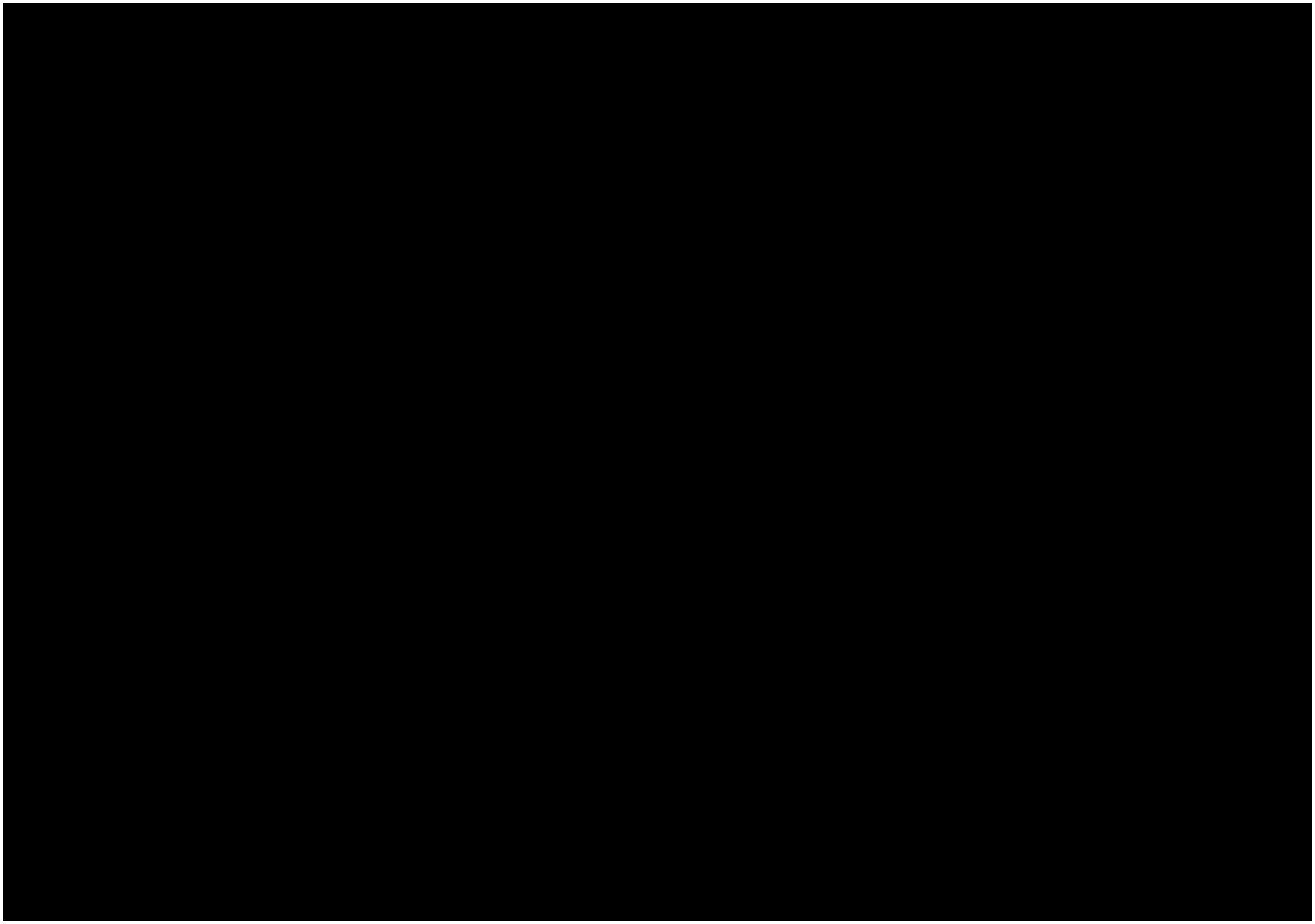
[b] Subjects should be instructed to not take pain medication for 12 hours before all study visits in Part B except for the 28-day follow-up visit (Visit B15).

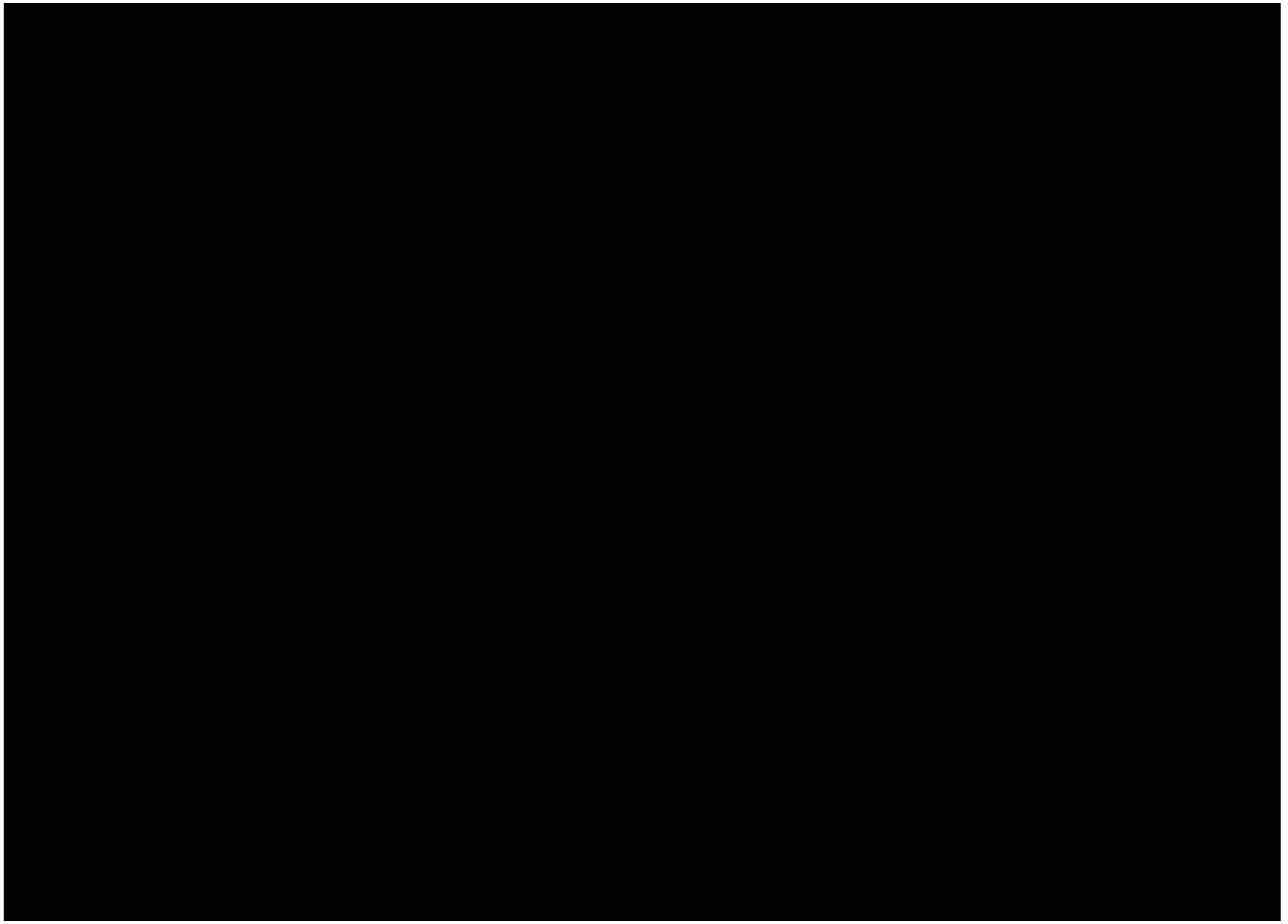
[c] If the difference in UPCR values between the two 24-hour urine collections for Visits B7 and B14 is > 20%, a third 24-hour urine will be collected to determine the average; this third sample should be collected as soon as possible but no more than 10 days after the first two results are reported.

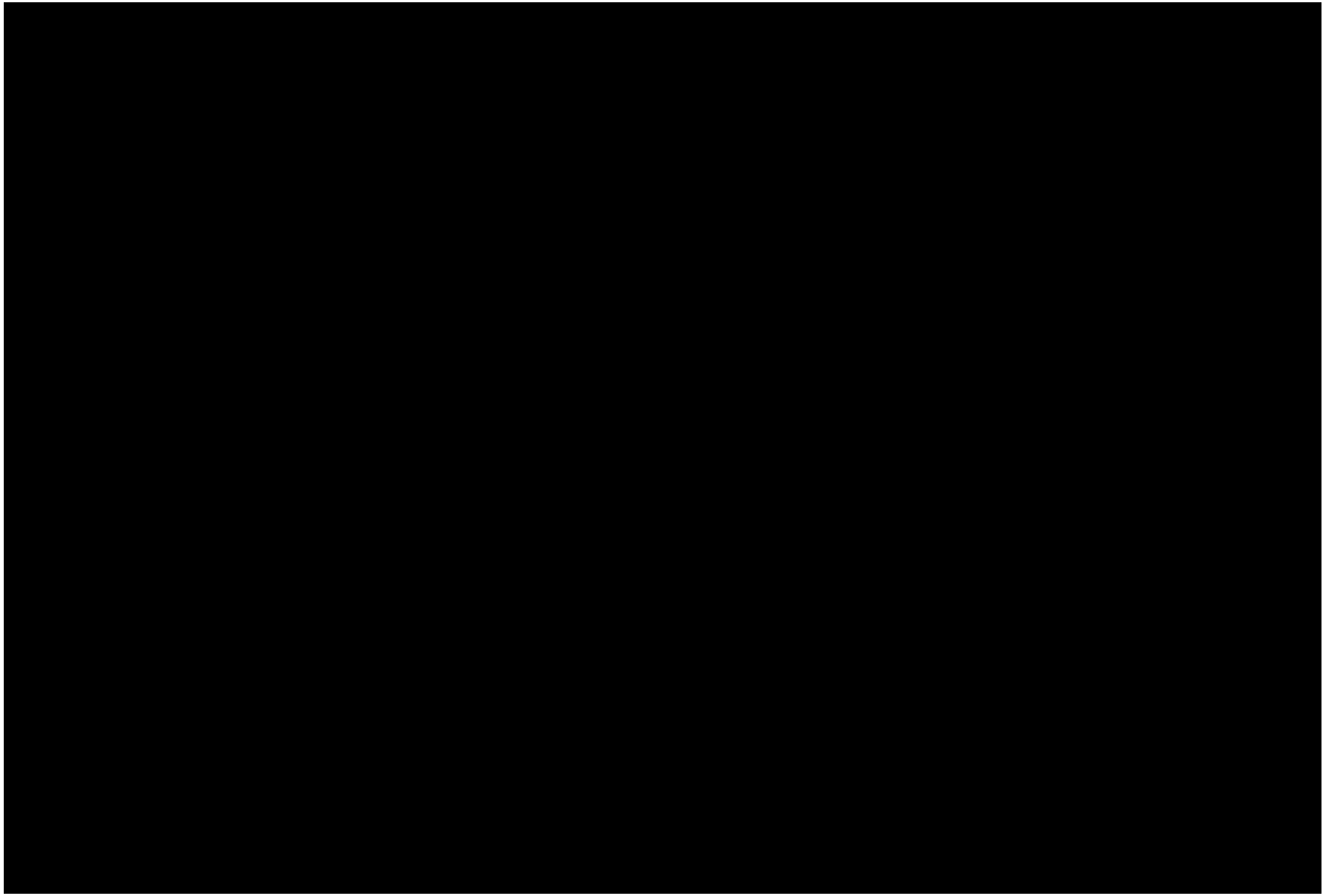
[d] Only subjects continuing to the LTE Period will be issued MMF and blinded study treatment at the Week 52 visit for Week 52 through Week 56.

Note: Unless they withdraw consent for follow-up, randomized subjects who discontinue the IP early will remain in the study for follow-up purposes including Visit B15; these subjects will be assessed on a case-by-case basis regarding the optional end-of-study renal biopsy.

Note: For premenopausal women, study visits and 24-hour urine collections should be scheduled, when possible, for when they are not menstruating.







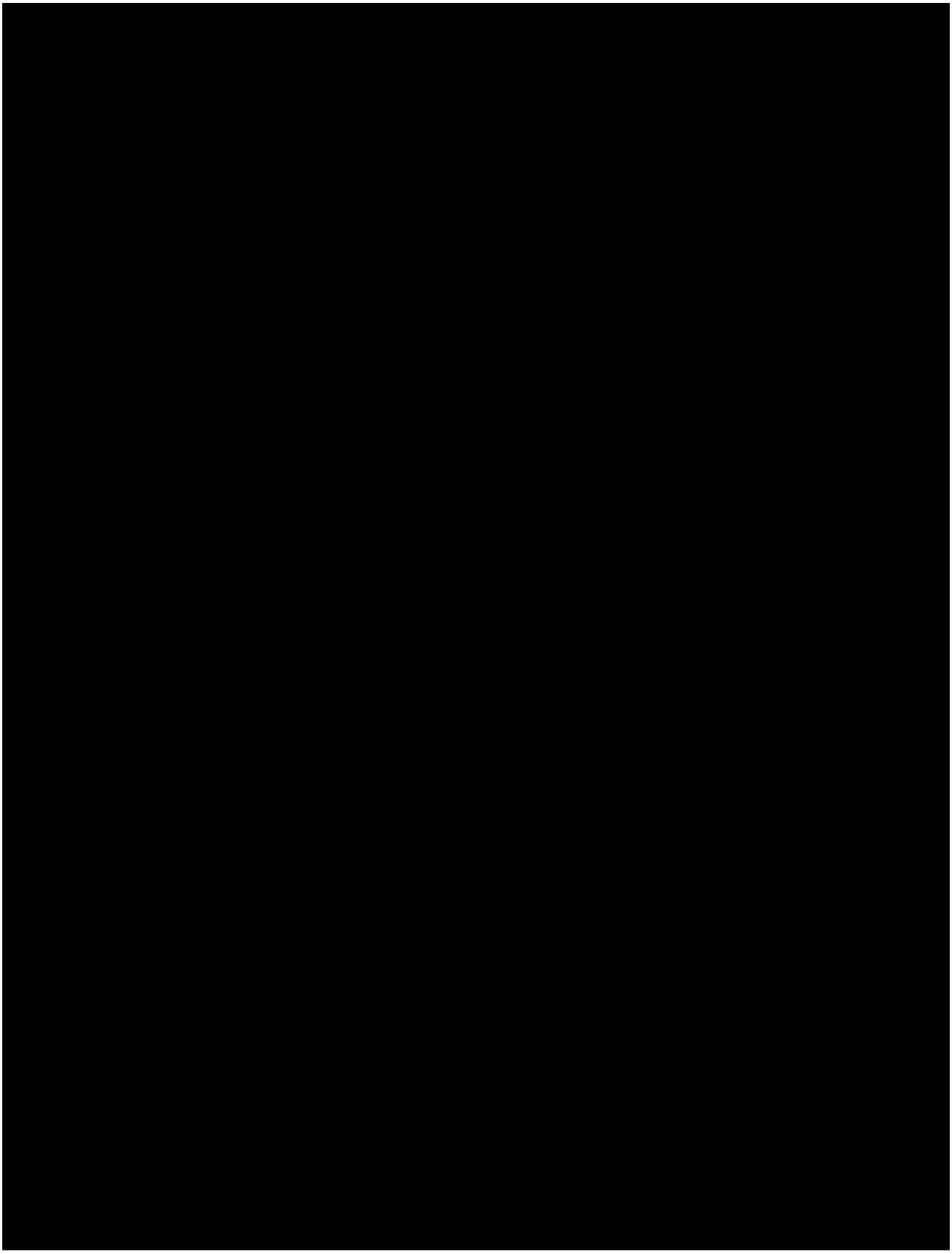
2 INTRODUCTION

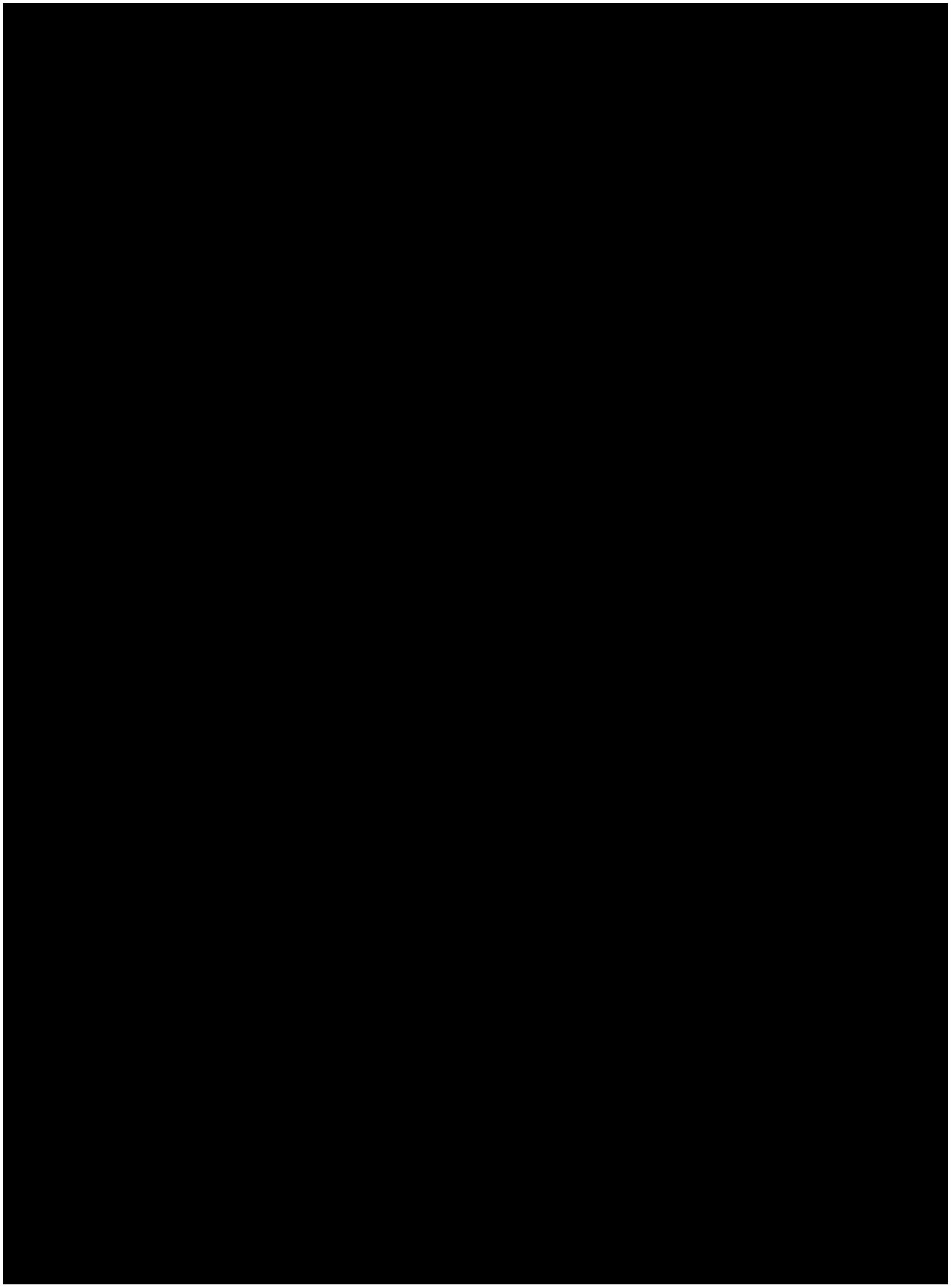
2.1 Study Rationale

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE). Approximately 38% of patients have LN at the time of SLE diagnosis and 10 to 20% of them may progress to end-stage renal disease. Lupus nephritis confers an almost 3-fold higher risk of death than SLE without LN.[6]

Despite advances in medical care, the prognosis for patients with LN has not substantially changed since the 1980s.[2] Although the current standard of care treatments may result in a little more than half the patients showing some improvement in certain markers of disease activity (such as proteinuria, serum creatinine, hematuria, and urinary casts),[7] long-term maintenance therapies are known to have toxic side effects and disease relapse is common.[8] There remains an unmet need for novel, well tolerated orally administered therapies that can effectively modify the disease course and control symptoms.

[redacted]



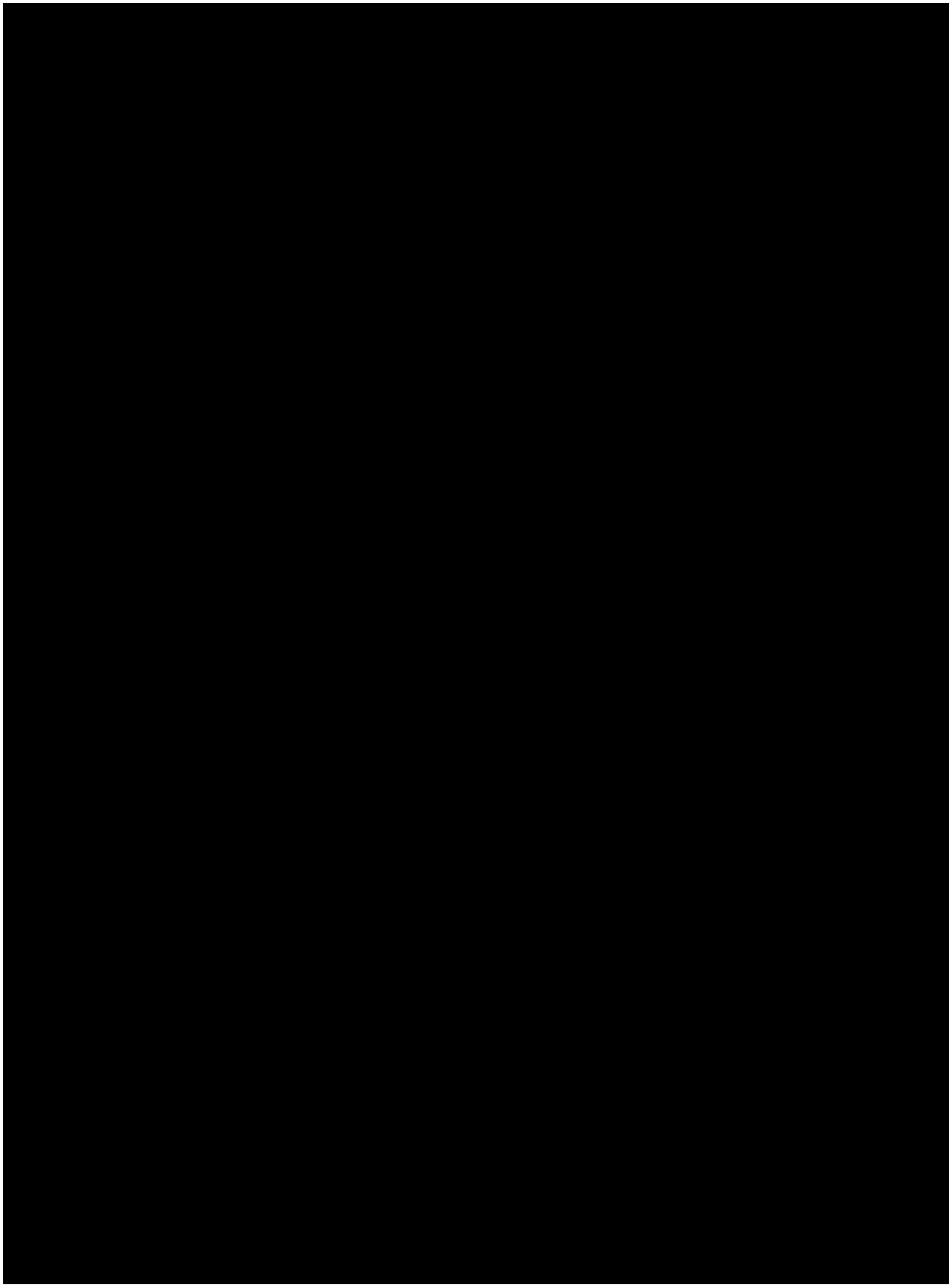


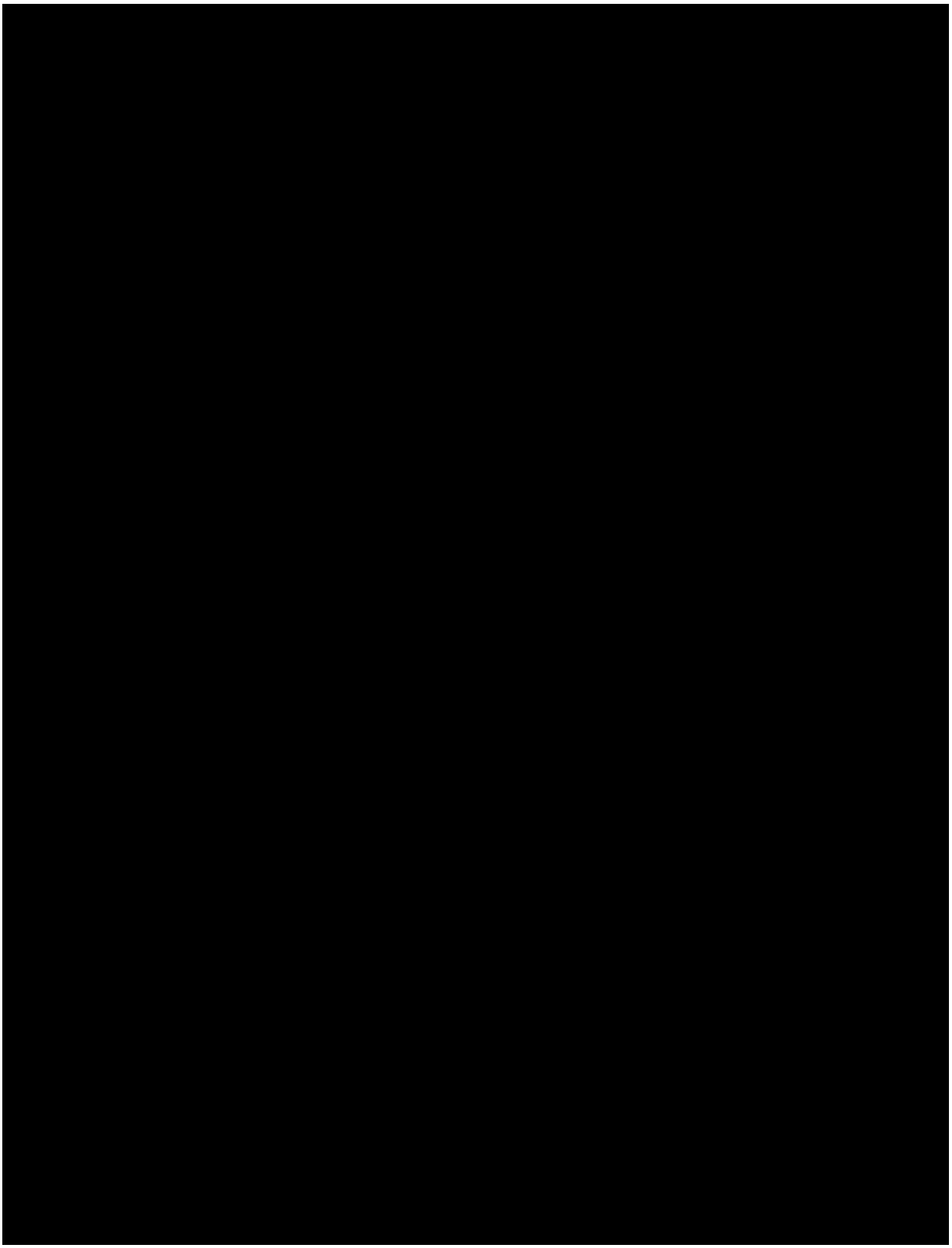
[redacted]

3 OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary – 52-week Blinded Treatment Period (Part B)	
• Safety: To assess the safety and tolerability of BMS-986165 in subjects with LN	• AEs, vital signs, ECGs, and laboratory abnormalities from baseline through Week 52
• Efficacy: To evaluate the efficacy of BMS-986165 compared with placebo with regard to proteinuria	• Percentage change from baseline in 24-hour UPCR at Week 24
Secondary– 52-week Blinded Treatment Period (Part B)	
• Efficacy: To evaluate the efficacy of BMS-986165 with regard to measures of renal function and SLE activity	• PRR at Week 24, defined as ≥ 50% reduction from baseline in 24-hour UPCR • CRR at Week 24, defined as both of the following: – 24-hour UPCR ≤ 0.5 mg/mg – eGFR ≥ 60 mL/min or ≤ 20% decrease from baseline • CRR at Week 52 • CRR + successful CS taper to ≤ 7.5 mg/day at Week 24 • CRR + successful CS taper to ≤ 7.5 mg/day at Week 52 • PRR at Week 52

[redacted]





AE = adverse event; C = complement; CRR = complete renal response; CS = corticosteroid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; NIH = National Institutes of Health; OSS = Ohio SLE Study; PRR = partial renal response; UPCR = urine protein:creatinine ratio

Note: 24-hour urine specimens will be used for the UPCR at baseline (Visit A4), Week 24 (Visit B7), and Week 52 (Visit B14).

Note: eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation

4 STUDY DESIGN

4.1 Overall Design

This is a 3-part, multicenter, randomized, double-blind study to evaluate the efficacy and safety of BMS-986165 in combination with background treatment with MMF in subjects with LN International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III or IV (alone or in combination with Class V). Subjects will be assessed for renal response after having received a total of at least 12 weeks (but ≤ 24 weeks) of treatment with MMF at a target dose of 1.5 to 3.0 g/day (refer to Section 6.1 for further details regarding individual target dose). Subjects will receive 12 weeks of target-dose MMF in Part A of the study if they have not been taking target-dose MMF at screening. Subjects who have been taking target-dose MMF for ≥ 1 day but < 12 weeks at screening will continue to receive target-dose MMF in Part A until they reach 12 weeks of total MMF treatment. Subjects who have been taking target-dose MMF for ≥ 12 weeks but ≤ 24 weeks at screening will enter the study at Visit A4 to immediately be assessed for renal response and entry into Part B.

Subjects with an inadequate renal response to MMF may be randomized to blinded study treatment BMS-986165 3 mg BID, BMS-986165 6 mg BID, or placebo BID, as add-on therapy to MMF in Part B. Inadequate response is defined as < 50% reduction in 24-hour urine protein:creatinine ratio (UPCR) from the pre-MMF value (refer to Section 4.1.2.2) and a 24-hour UPCR ≥ 1.0 mg/mg. Randomized subjects will continue taking open-label MMF with or without corticosteroids. Randomization will be stratified by baseline (Visit A4) 24-hour UPCR (< 3.0 mg/mg versus ≥ 3.0 mg/mg) and total cumulative intravenous (IV) corticosteroid (IV methylprednisolone or

parenteral equivalent) dose given in the 16 weeks before randomization (< 250 mg versus ≥ 250 mg).

The total duration of participation in the study is up to [redacted] weeks, which includes the following periods:

- Screening period: approximately 28 days (this period may be extended up to 5 days if needed to complete screening procedures, with approval of the [redacted] medical monitor)
- Treatment period:
  - Part A: Open-label MMF (1.5 to 3.0 g/day) run-in period of up to 12 weeks, depending on duration of treatment with MMF at the time of screening; see Table 2 for the assessments during Part A
  - Approximately 1 week between the last visit in Part A (Visit A4) and the first visit in Part B (Visit B1)
  - Part B: Randomization followed by blinded study treatment for 52 weeks plus continued open-label MMF with or without corticosteroids (or just continued open-label MMF with or without corticosteroids for those who are not randomized); all subjects will attend study visits every 4 weeks and undergo assessments as indicated in Table 3
  - [redacted]
- A follow-up period of 28 ± 3 days followed by an end-of-study visit

After a screening period of up to 28 days, eligible subjects will enter Part A of the study, an open-label MMF run-in period of up to 12 weeks. Subjects may continue taking MMF as previously prescribed (if at a dose of 1.5 to 3.0 g/day) until they reach 12 weeks of treatment or, if not receiving MMF or previously prescribed < 1.5 g/day, subjects will be either started on MMF when they enter Part A or titrated to a dose of 1.5 to 3.0 g/day for the full 12 weeks of Part A. Subjects who have been taking MMF at a dose of 1.5 to 3.0 g/day for ≥ 12 but ≤ 24 weeks at the time of screening will promptly be evaluated for continuation in Part B and for randomization. The suggested target dose of MMF at the first visit in Part B is 1.5 to 2.0 g/day (maximum 3.0 g/day) unless limited by intolerance or toxicity (refer to Section 6.1 for further details regarding individual target dose).

After at least 12 weeks of open-label MMF treatment of at least 1.5 g/day (either only during Part A of the study or including previously prescribed MMF before and during screening), subjects

will be assessed to determine whether they meet the criteria to continue in Part B (see Section 4.1.2.1), and whether they meet the randomization criteria (see Section 4.1.2.2). Those subjects who meet all the criteria to continue in Part B and meet the randomization criteria will be assigned in a double-blind manner (1:1:1) to one of the following treatment groups:

- BMS-986165 3 mg BID + continued open-label MMF with or without corticosteroids
- BMS-986165 6 mg BID + continued open-label MMF with or without corticosteroids
- Placebo BID + continued open-label MMF with or without corticosteroids

Randomization will be stratified by baseline (Visit A4) 24-hour UPCR (< 3.0 mg/mg versus ≥ 3.0 mg/mg) and total cumulative IV corticosteroid (IV methylprednisolone or parenteral equivalent) dose given in the 16 weeks before randomization (< 250 mg versus ≥ 250 mg).

Subjects who meet the criteria to continue in Part B but do not meet the randomization criteria may continue on open-label MMF with or without corticosteroids during Part B and will attend the same visits every 4 weeks and have the same assessments as randomized subjects. These nonrandomized subjects will exit the study at the end of Part B.

Corticosteroids are permitted but not required in this study. Subjects who are taking corticosteroids will have their dose tapered (if possible) during Part B as described in Section 6.6.1.

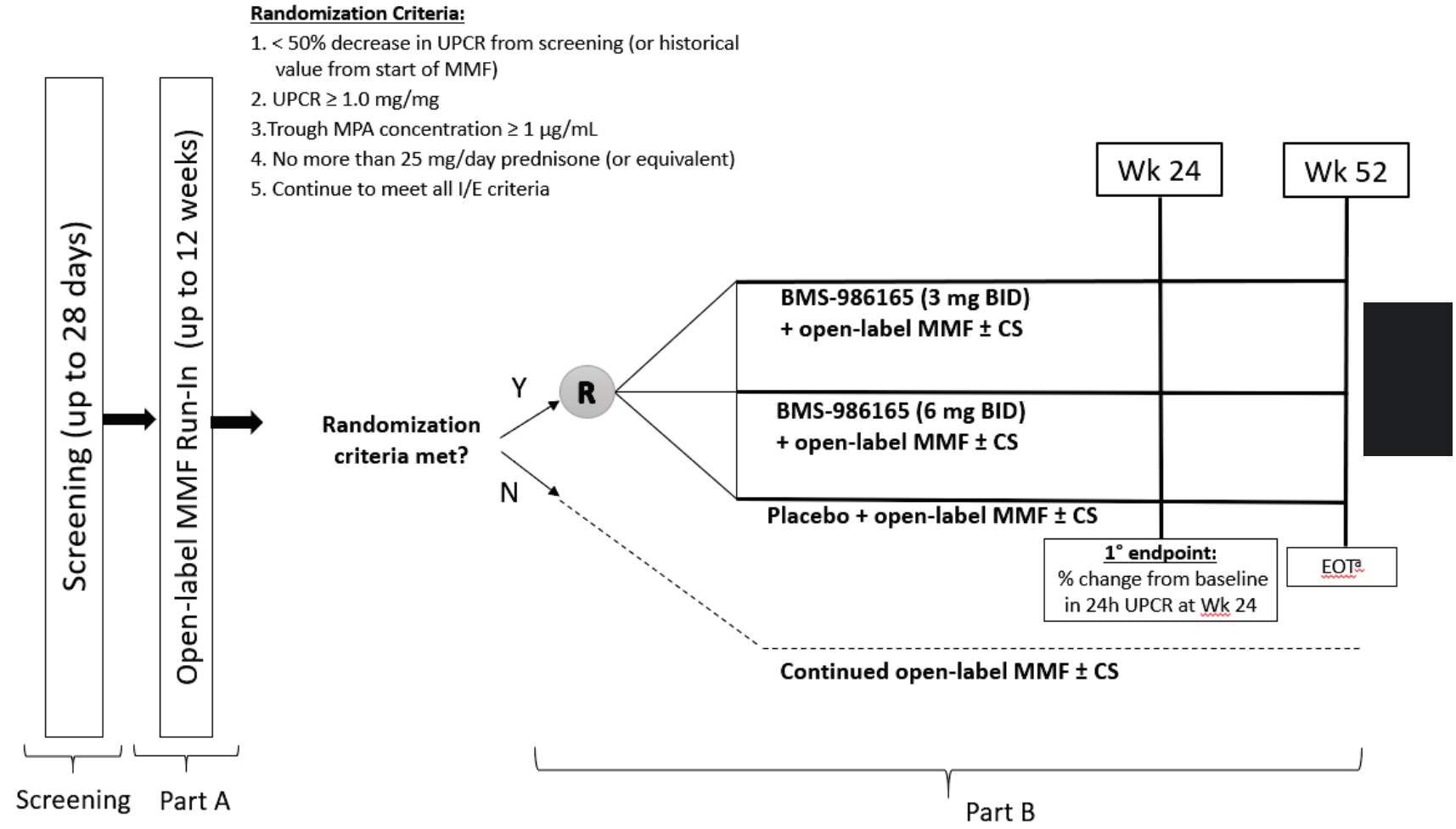
In Part B, subjects (randomized and nonrandomized) will attend study visits every 4 weeks through Week 52. [redacted]

Optional renal biopsies may be performed at Week 52 [redacted], as well as at the end of treatment for subjects who discontinue early if discontinuation occurs after Week 24 of Part B. After the last treatment visit (Week 52[redacted] or early discontinuation), subjects will attend a final end-of-study visit at the end of a 28-day follow-up period.

The study design schematic is presented in Figure 1.

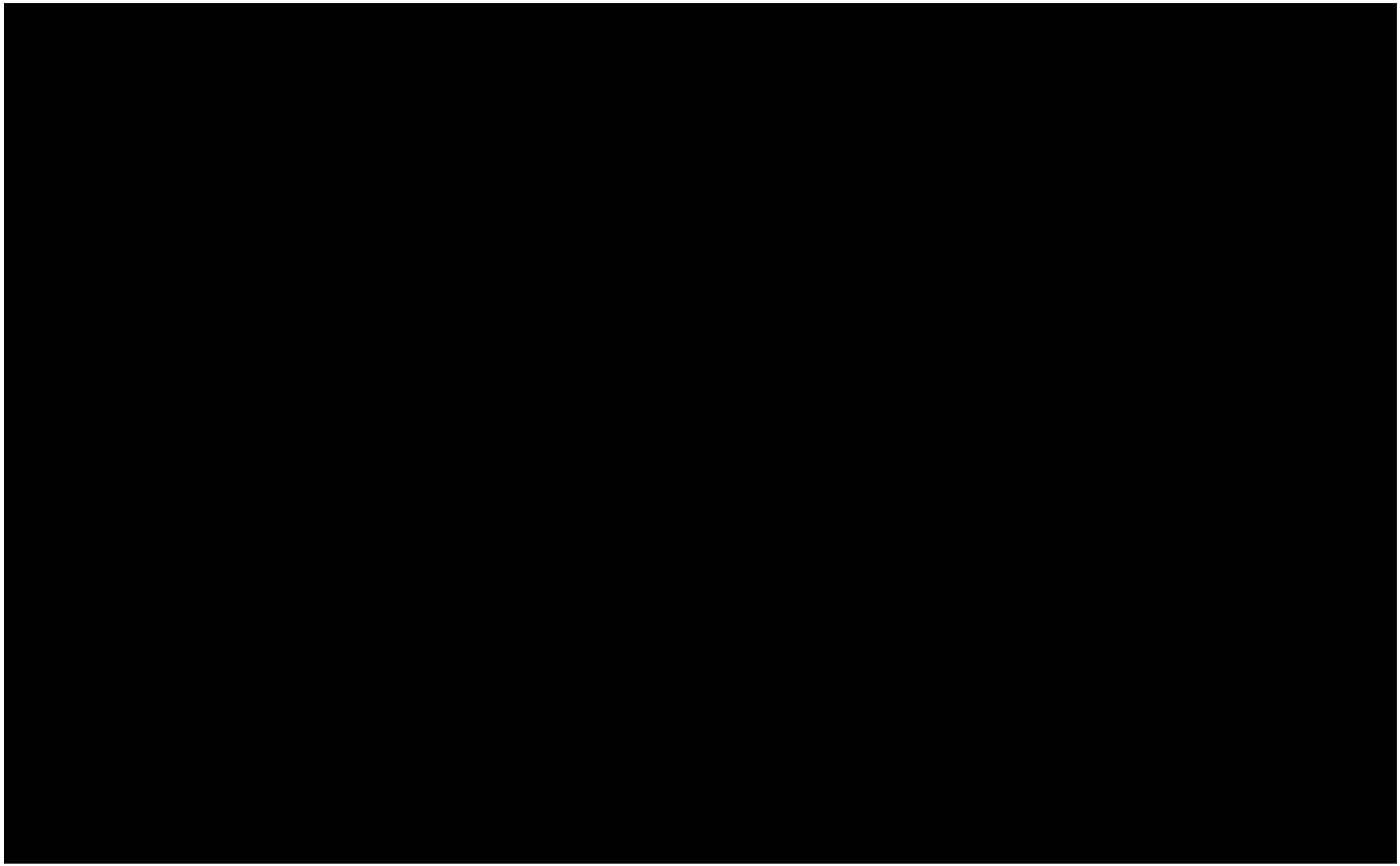
Figure 1: Study Design: Part A and Part B

The study design schematic for the open-label MMF run-in period (Part A) and the 52-week Blinded Treatment Period (Part B) is presented below.



[redacted]

BID = twice daily; CS = corticosteroid; EOS = end-of-study; EOT = end-of-treatment; d = day; F/U = follow-up; I/E = inclusion/exclusion; LTE = Long-term Extension; MMF = mycophenolate mofetil; MPA = mycophenolic acid; PRR = partial renal response; R = randomization; UPCR = urine protein:creatinine ratio; Wk = week



4.1.1 Part A: Open-label Mycophenolate Mofetil Run-in Period

All subjects who meet the study eligibility criteria will enter Part A of the study.

Subjects who are not already taking MMF will begin MMF and titrate to a dose of 1.5 to 3.0 g/day, and subjects who are taking < 1.5 g/day of MMF at screening will increase to a target dose of 1.5 to 3.0 g/day (refer to Section 6.1 for further details about individual target dose) with or without corticosteroids. After 12 weeks of treatment with MMF at a dose of 1.5 to 3.0 g/day, they will be evaluated for continuation in Part B and for randomization.

Subjects who have been taking MMF at a dose of 1.5 to 3.0 g/day for ≥ 1 day but < 12 weeks at the time of screening will continue MMF in Part A until they have completed a total of 12 weeks of treatment at this dose (including weeks of MMF before entering Part A), and will then be evaluated for continuation in Part B and for randomization.

Subjects who have been taking MMF at a dose of 1.5 to 3.0 g/day for ≥ 12 but ≤ 24 weeks at the time of screening will promptly be evaluated for continuation in Part B and for randomization (Visit A4; including collection of a single 24-hour urine specimen; the other UPCR value will be the one from the 24-hour urine at screening) as soon as eligibility is confirmed.

Subjects who have been taking MMF at a dose of 1.5 to 3.0 g/day for > 24 weeks at the time of screening are not eligible to participate in the study.

Paths to enrollment based on the duration of MMF treatment at a dose of 1.5 to 3.0 g/day at the time of screening are shown in Figure 3 and Figure 4.

Subjects will attend up to 4 visits in Part A:

- Visit A1 (Day 1)
- Visit A2 (Week 4 of MMF ± 14 days)
- Visit A3 (Week 8 of MMF ± 14 days)
- Visit A4 (Week 12 of MMF ± 14 days)

  Note: The ±14-day windows for Visit A2, Visit A3, and Visit A4 are used to allocate the subject's first Part A visit based on the subject's number of weeks on MMF; the actual visit dates subsequent to the first Part A visit should occur as close to the required timepoint (Week 4, Week 8, or Week 12) as possible, with a ±3 day window to complete the visit.

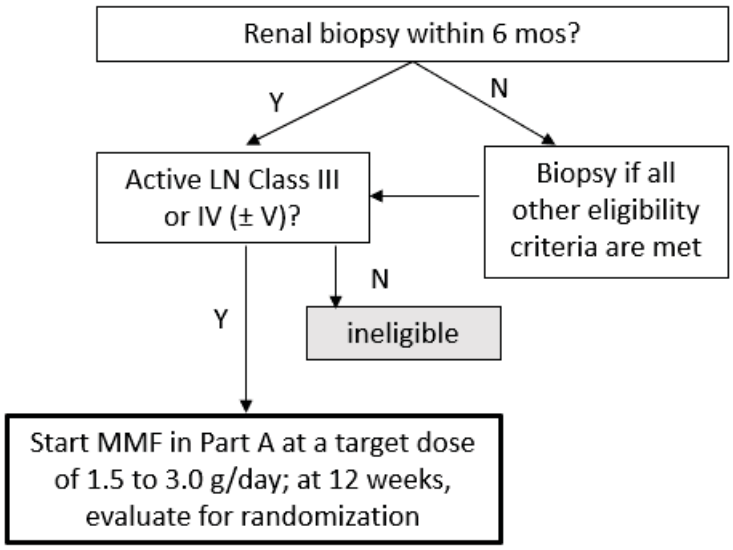
Subjects who are not taking MMF during screening or who are taking < 1.5 g/day will attend all 4 visits in Part A. Subjects with ≥ 1 day but < 12 weeks of MMF at a dose of 1.5 to 3.0 g/day will continue their MMF treatment until they reach the corresponding Part A visit (A2, A3, or A4). Subjects whose duration of MMF therapy puts them between two Part A visits will "round up" to the next visit. For example, a subject with 6 weeks of MMF when entering Part A would start at Visit A3.

Subjects with ≥ 12 but ≤ 24 weeks of MMF at a dose of 1.5 to 3.0 g/day at the time of screening will enter Part A and attend Visit A4 to be assessed for continuation in Part B and for

randomization as soon as possible after study eligibility is confirmed. No subject will "round up" to Visit A4 unless they meet the minimum of 12 weeks ± 3 days of MMF as shown in Table 2.

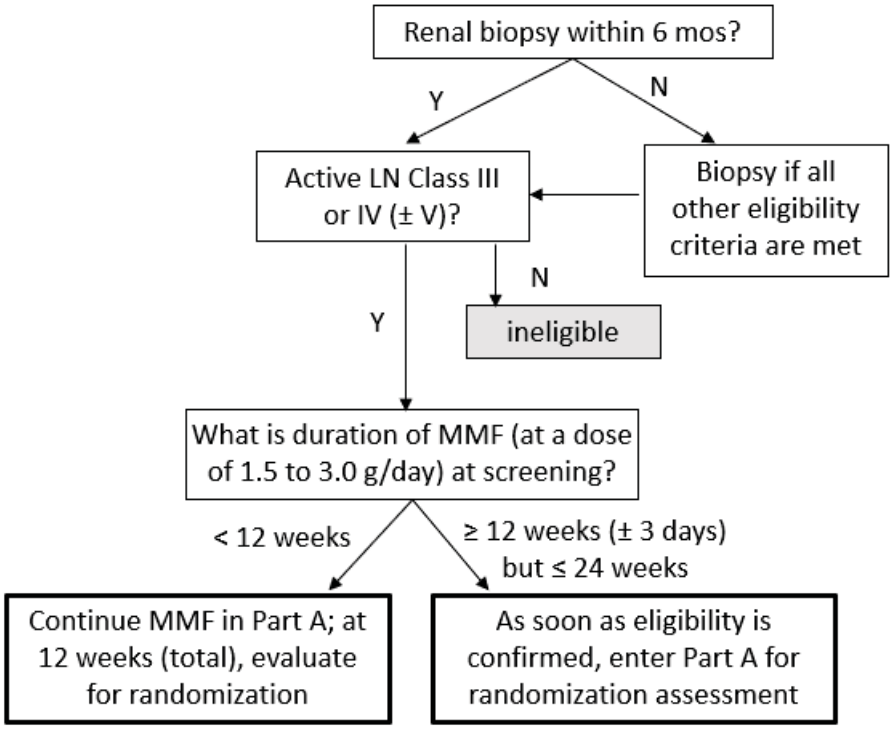
For premenopausal women, study visits and 24-hour urine collections should be scheduled, when possible, for times when they are not menstruating.

Figure 3: Path to Enrollment for Subjects Not Taking Mycophenolate Mofetil or Who Are Taking Less Than 1.5 g/day at the Time of Screening



LN = lupus nephritis; MMF = mycophenolate mofetil; mos = months

Figure 4: Paths to Enrollment for Subjects with ≥ 1 Day but ≤ 24 Weeks of Mycophenolate Mofetil at a Dose of 1.5 to 3.0 g/day at the Time of Screening



LN = lupus nephritis; MMF = mycophenolate mofetil; mos = months

4.1.1.1 Evaluation for Continuation in Part B and for Randomization

When subjects have completed 12 weeks of MMF treatment at a dose of 1.5 to 3.0 g/day, they will attend Visit A4 and will have assessments needed to determine whether they meet the criteria to continue in Part B and the randomization criteria. Samples and assessments will include the following:

- Spot UPCR from a first morning voided specimen (a second morning void may be used if the first morning void was not collected)
- Two 24-hour urine specimens (one approximately 7 to 10 days before Visit A4 and the other just before Visit A4); if the UPCR values between these specimens differ by > 20%, a third 24-hour urine specimen will be collected to determine the average value; the third sample (if needed) should be collected as soon as possible but no more than 10 days after the first two results are reported
- Trough plasma mycophenolic acid (MPA) concentration
- Investigator determination of whether subject is taking and tolerating target-dose MMF (1.5 to 3.0 g/day) and likely to continue to tolerate the target dose through Week 52

For subjects with 12 to 24 weeks of MMF at a dose of 1.5 to 3.0 g/day at the time of screening, a 24-hour urine specimen should be collected and Visit A4 should occur as soon as possible after eligibility is confirmed so that they will not exceed 28 weeks of MMF at a dose of 1.5 to 3.0 g/day at the time of randomization. Because 2 to 4 weeks may be required to complete the screening evaluations to determine eligibility to participate in the study, these subjects will likely have the randomization assessment visit at Week 26 or 27 of MMF, and the randomization visit (Visit B1) no later than 28 weeks of MMF. For these subjects, their UPCR for randomization will be calculated from the 24-hour urine specimens collected at screening and Visit A4.

4.1.2 Part B: Randomized, Blinded Treatment Period Through Week 52

No more than 10 days after Visit A4, subjects should attend the randomization visit (Visit B1). Medical monitor approval is required if more than 10 days is necessary. At this visit, the laboratory results from Visit A4 will be evaluated to determine whether the subject meets the criteria to continue in Part B, and whether they meet the randomization criteria.

Subjects who do not meet the criteria to continue in Part B will exit the study.

Subjects who meet the criteria to continue in Part B but do not meet the randomization criteria may continue on open-label MMF.

Subjects who meet the criteria to continue in Part B and the randomization criteria will be randomized to blinded study treatment plus continued MMF.

For premenopausal women, study visits and 24-hour urine collections should be scheduled, when possible, for times when they are not menstruating.

All subjects in Part B will then attend study visits every 4 weeks (± 3 days) through Week 52.

4.1.2.1 Criteria to Continue in Part B With or Without Randomization

1. Trough MPA concentration ≥ 1 µg/mL (this sample will be collected at Visit A3 to allow sufficient time for analysis and reporting of result; for subjects with ≥ 12 weeks of MMF at the time of screening, the screening value will be used)
2. The corticosteroid dose (if any) at Visit B1 must not exceed 25 mg/day of prednisone (or equivalent dose of other corticosteroid; see APPENDIX 6)
3. The subject continues to meet all study eligibility criteria (see Section 5), including the blood pressure requirement (see Exclusion Criterion 2b in Section 5.2)
4. The subject is taking and tolerating target-dose MMF (1.5 to 3.0 g/day) and likely to continue to tolerate the target dose through Week 52

4.1.2.2 Randomization Criteria

Subjects who meet the criteria to continue in Part B and meet the following criteria will be eligible to be randomized to add-on therapy with blinded study treatment:

1. < 50% reduction in UPCR from the pre-MMF value (either the value from study screening or historical value before the start of MMF for those already on MMF at the time of screening) to the value at Visit A4. For the subjects who are on MMF at a dose of < 1.5 g/day at the time of screening, the pre-MMF value will be taken from screening
2. UPCR ≥ 1.0 mg/mg based on the two 24-hour urine specimens from approximately 7 to 10 days before Visit A4, and just before Visit A4; if the UPCR values differ by > 20%, a third 24-hour urine specimen will be collected to determine the average; the third specimen (if needed) should be collected as soon as possible but no more than 10 days after the first two results are reported, as described in Section 8.4.1

[redacted]

4.1.4 Post-treatment Follow-up

Within 2 weeks after completing 52 weeks [redacted] of blinded study treatment, randomized subjects will have the option to have an end-of-treatment renal biopsy. Subjects who discontinue

early will also have the option to have an end-of-treatment renal biopsy, if discontinuation occurs after Week 24 of Part B. At the end of a 28-day (± 3 days) post-treatment follow-up period, subjects will attend an end-of-study visit.

4.1.5 Data Monitoring Committee

An external DMC with multi-disciplinary representation will be established to evaluate on a periodic basis AEs, laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. The DMC responsibilities, authorities, and procedures will be documented and followed according to the DMC charter.

4.1.6 Central Review Services

Central Review Services (CRS) will be used in this study. The scope of responsibility will include, but will not be limited to, review of lupus-related eligibility criteria, flares, and cross-validation of the instruments used in this study to assess disease activity and progression. Further details on the content and methods of data reports by CRS will be outlined in the Central Review Plan, as will the processes and procedures to be followed.

4.2 Number of Subjects

A sufficient number of individuals will be screened so that approximately 78 subjects will be randomized in Part B of the study (52 subjects in the combined BMS-986165 groups and 26 subjects in the placebo group).

4.3 End-of-Study Definition

The duration of study participation for individual subjects may be up to [redacted] weeks ([redacted] days).

The start of the study is defined as the first visit for the first subject screened. The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 1.3) for the last subject. Study completion is defined as the final date on which data were or are expected to be collected. [redacted]

4.4 Scientific Rationale for Study Design

4.4.1 Rationale for Overall Study Design

The objectives of this study are to evaluate the efficacy and safety of BMS-986165 in subjects with ISN/RPS[1] Class III or IV (alone or in combination with Class V) LN. A placebo control is included to allow the effects of treatment both desired and adverse, to be appropriately attributed to treatments received. The use of a placebo group is balanced by the fact that all subjects will continue concomitant background treatment with MMF, with or without corticosteroids, which are standard-of-care treatments for patients with LN.

The eligibility criteria have been designed to minimize the risk for serious infections that may be associated with immunosuppressive therapies.

The protocol includes a plan for corticosteroid tapering at regular intervals during Part B to assess whether the effects of BMS-986165 on renal function allow for reduction of the corticosteroid

dose and associated complications. The protocol has a provision for a single corticosteroid rescue, provided the dose can then be tapered down within 2 weeks.

Safety and efficacy results will be assessed throughout the study to allow timely management of any concerns that arise. Subjects will attend study visits every 4 weeks [redacted] and will be closely monitored for AEs. A DMC will monitor safety and efficacy findings throughout the study to allow timely management of any concerns that could arise. Use of the Revised Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Flare Index (rSFI)[11] and Ohio SLE Study (OSS) Flare Index[10] in addition to frequent clinical and laboratory assessments will allow prompt detection of disease flare so subjects can be properly managed with regard to their disease, and to accurately assess the renal response.

4.4.2 Rationale for 12-Week Mycophenolate Mofetil Run-in Period

The inclusion of the open-label MMF run-in period is based on the risk for further deterioration of renal function in patients with LN who fail to respond to aggressive induction therapy with immunosuppressive drugs, usually with MMF or cyclophosphamide. Even with MMF treatment, there is only a 50% to 60% rate of complete or partial response to induction therapy.[12] In this study, subjects who do not respond adequately to MMF after 12 to 24 weeks will be randomized to one of the BMS-986165 treatment groups or placebo, to assess whether add-on therapy might enhance the renal response.

Studies have shown that even 10 years following induction treatment for LN, many patients continue to require immunosuppressants and/or corticosteroids.[13] Given the many adverse effects of corticosteroids and their contribution to organ damage in patients with SLE, it is essential to identify effective steroid-sparing regimens as early as possible.[14]

The 10-year results from the MAINTAIN trial showed that proteinuria decreased more promptly in patients who had good long-term renal outcomes (as assessed by GFR and/or creatinine) than in those who had poor long-term renal outcomes.[15] The investigators found that proteinuria alone drove the long-term outcomes in these patients and also that values at baseline were not predictive of long-term outcomes. It has also been shown that patients who achieve urine protein levels of ≤ 1.5 g/day with maintenance of creatinine values within 25% of baseline have significantly better outcomes than patients who do not, although they do not do as well as patients who achieve complete remission.

Likewise, Houssiau et al showed that the positive predictive value (PPV) for good long-term renal outcome is 90% when there is a 50 to 75% reduction in proteinuria by 6 months and PPV is 87% in those with proteinuria less than 1 g/day. This trend was also noted by 3 months.[16] Korbet et al demonstrated that a 50% reduction in proteinuria at 6 months was predictive of favorable long-term outcomes with more stable renal function, less end-stage renal disease, and higher renal survival at 15 years.[17] Patients who achieved a 50% reduction were four times more likely to ultimately achieve complete remission.

Early response to treatment in LN also has important implications in terms of damage. Hanaoka et al showed that patients who failed to achieve partial renal response (PRR) at Week 12 had more damage by the Systemic Lupus Erythematosus International Collaborating Clinics

(SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) at 3 years versus patients who did achieve PRR at Week 12, regardless of whether they achieved complete response at 1 year.[18]

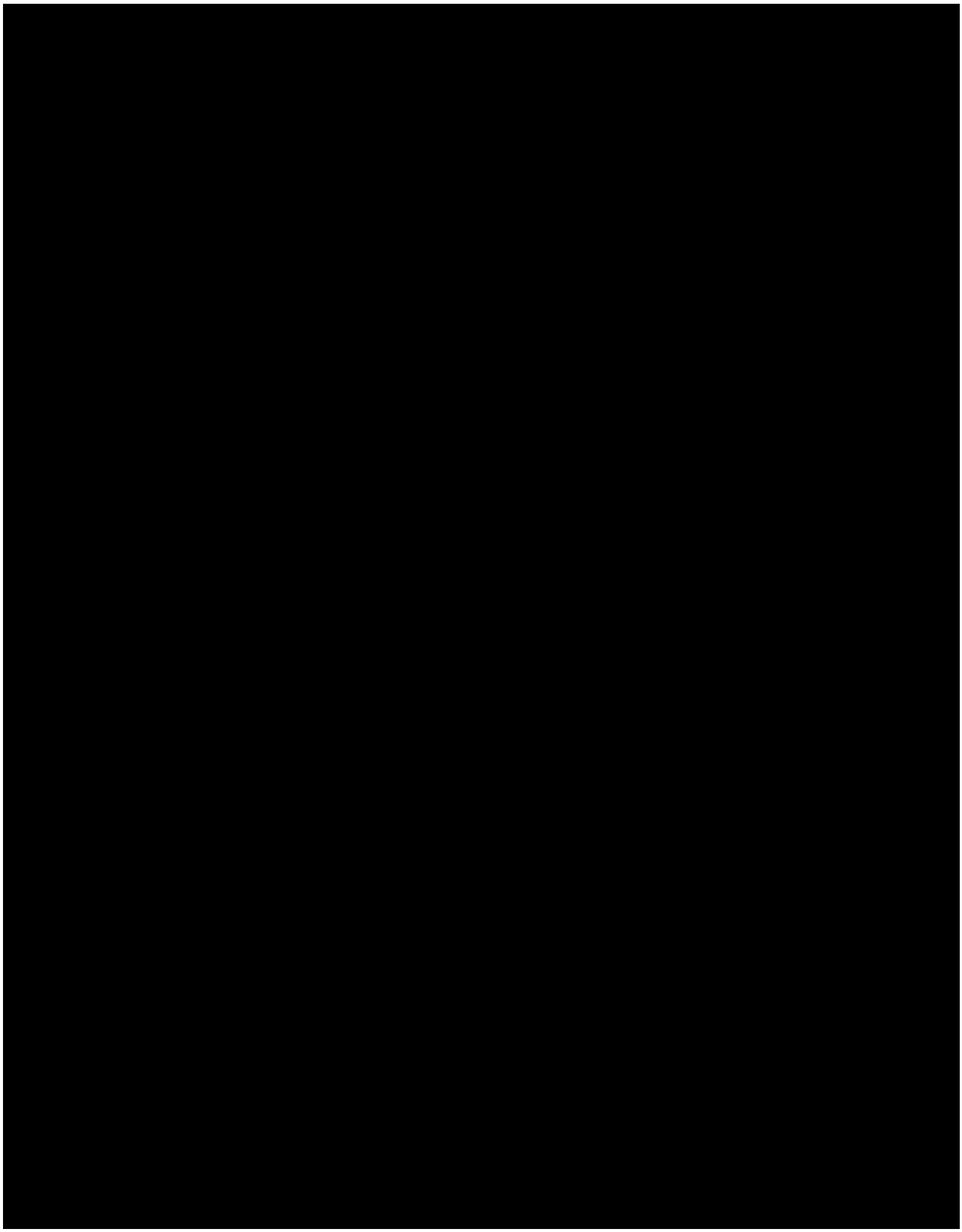
Current guidelines recommend treatment of patients with LN with either cyclophosphamide or MMF plus corticosteroids followed by lower-dose maintenance therapy if they have responded, or by a change in therapy if they have not.[19, 20] Complete renal response can take up to 2 years to reach with < 30% to 40% of patients achieving this outcome within the first 6 months of treatment. Switching to an alternative agent is recommended for patients who fail to improve within 3 to 4 months, or do not achieve a PRR after 6 to 12 months, or a complete renal response within 2 years of treatment.[14]

Given the importance of proteinuria reduction and the implications of early response on long-term outcomes in patients with LN, this study will look at the use of BMS-986165 as add-on therapy in subjects who do not achieve at least a 50% reduction in proteinuria or reduction in proteinuria within 24 weeks of starting MMF or increasing to an MMF dose of 1.5 g/day or higher in hopes of improving the response in these subjects with an inadequate or incomplete response to standard LN induction therapy.

4.4.3 Rationale for Optional Week 52, [redacted] and Early Discontinuation Renal Biopsies

To better understand the true impact of BMS-986165 on the pathophysiology of LN, an optional renal biopsy may be performed at Weeks 52 [redacted], as well as at the end of treatment for subjects who discontinue early, if discontinuation occurs after Week 24 of Part B. Studies have shown that patients in clinical remission (ie, partial or complete reduction in proteinuria) but with residual histologic activity are at increased risk for subsequent flares versus those who are in histologic remission.[21] Renal biopsy is the gold standard not only for diagnosing LN but also for identifying cellular features that drive the aggressiveness of management. Because of the well-known discrepancy between clinical markers such as the degree of proteinuria and biopsy findings,[22] it is also important to assess the histologic response to treatment. In addition to identifying cellular changes with treatment, repeat biopsy at 52 [redacted] weeks (and/or early discontinuation, if applicable) will aid in identifying changes in the class of nephritis and degree of ongoing active inflammation versus fibrosis and tubular atrophy. This analysis is also important in guiding subsequent treatment decisions and identifying those who continue to require more aggressive immunosuppressant therapy or who may require a change in the type of treatment being prescribed after the end of the treatment period for this study.

[redacted]



5 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used to assess the endpoints. It is imperative that subjects fully meet all eligibility criteria.

All screening and randomization evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Central reviewers along with the [redacted] medical monitor will review all eligibility criteria for all subjects who are not initially screen-failed by the site. No subject will be randomized without confirmation of eligibility by CRS and the [redacted] medical monitor.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of informed consent may be utilized for screening purposes, provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in Section 1.3. Unless otherwise specified, all laboratory testing must be performed by the central laboratory.

The screening period is up to 28 days. If the eligibility parameters cannot be obtained within that time, the screening period may be extended up to 5 days if approved by the [redacted] medical monitor.

To be eligible for the study, subjects must meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1) Signed Written Informed Consent

a. Willing to participate in the study and have the ability to give informed consent
b. Willing and able to complete all study-specific procedures and visits

2) SLE Disease Characteristics

a. Meets the SLICC criteria for SLE (see APPENDIX 5)
b. Renal biopsy confirming a histologic diagnosis of active LN ISN/RPS Classes III (A or A/C), IV-S (A or A/C), or IV-G (A or A/C); or Class V (in combination with Class III or IV) (see APPENDIX 12):
    i. N/A per Revised Protocol 10
    ii. N/A per Revised Protocol 10
    iii. If a biopsy was done within ≤ 6 months before screening, sites/laboratories have the option of providing at least one of the following samples: Renal fresh biopsy; renal historical biopsy (Formalin Fixed Paraffin Embedded block); renal archival slides; or digital image slides (refer to the Arkana laboratory manual for further details)
    iv. If a biopsy has not been done within 6 months before screening and the subject meets all other eligibility criteria, a biopsy will be performed as part of the study
c. N/A per Revised Protocol 10

d. UPCR ≥ 1.5 mg/mg (for subjects with biopsies taken ≤ 6 months prior to screening) or UPCR ≥ 1 mg/mg (for subjects with biopsies taken ≤ 3 months prior to screening) assessed with a 24-hour urine specimen

3) Medications for SLE/Concomitant Medications

a. N/A per Revised Protocol 10

b. If subjects are taking an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or antimalarial drug, the dose must be stable for at least 4 weeks before randomization into Part B, with no anticipated changes in dosage in Part B

c. Required discontinuation periods for other immunomodulatory drugs or biologic drugs must be met as outlined in APPENDIX 7. If a specific drug is not listed, consult the [redacted] medical monitor for guidance; usual discontinuation periods are 4 weeks or 5 half-lives, whichever is longer

d. It is allowed but not required for prospective subjects to have been taking MMF for ≤ 24 weeks at the time of screening. The suggested target dose is 1.5 to 2.0 g/day (maximum 3.0 g/day) unless limited by toxicity or intolerance (refer to Section 6.1 for further details regarding individual target dose)

4) Age and Reproductive Status

a. Men and women aged 18 (or local age of majority) to 75 years inclusive at the time of screening

b. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin) at screening, within 24 hours before the first dose of MMF in Part A, and before the first dose of blinded study treatment in Part B.

c. Women must not be breastfeeding

d. The contraception requirements for MMF are stricter than those for BMS-986165; therefore the requirements for MMF (see APPENDIX 4) must be followed throughout study participation and for a period of time after the final dose of MMF or blinded study treatment as follows:

   i. WOCBP:
      a. Per the MMF prescribing information, subjects taking MMF must use acceptable contraception (see options in APPENDIX 4) throughout the study and continue for at least 6 weeks after the final dose of MMF
      b. Subjects must be counseled that MMF may reduce the effectiveness of oral contraceptives, and use of additional barrier contraceptive methods is required

   ii. Men who are sexually active with WOCBP:
      a. Subjects must inform any and all partners of their participation in the study and the need to use contraception during the man's study participation and for at least 90 days after his last dose of MMF
      b. Per the MMF prescribing information, male subjects taking MMF must continue to use effective contraception and should not donate sperm for at least 90 days after the final dose of MMF

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Target Disease

a. Pure ISN/RPS Class V membranous LN
b. Screening estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease [MDRD] equation) ≤ 30 mL/minute/1.73 m^2
c. N/A per Revised Protocol 10
d. History of kidney transplantation or planned transplantation during the study
e. End-stage renal disease
f. Autoimmune diseases other than SLE, with the exception of secondary Sjögren's syndrome, celiac disease, and stable Hashimoto's thyroiditis (based on normal thyroid-stimulating hormone [TSH], or if the TSH is abnormal at screening, a normal free thyroxine (T4); subjects with abnormal TSH and abnormal free T4 will be excluded, but after discussion with the [redacted] medical monitor may be able to rescreen a minimum of 6 weeks after adjustment of thyroid hormone replacement therapy)
g. SLE overlap syndromes such as mixed connective tissue disease or coexisting scleroderma or rheumatoid arthritis
h. Antiphospholipid Syndrome (APS):
    a. The following are exclusionary:
        i. Confirmed diagnosis of APS as defined by the Sapporo criteria (see APPENDIX 13) if there has been a thrombotic event or pregnancy morbidity within 12 months before screening
        ii. History of catastrophic APS (see APPENDIX 14)
    b. The following are not exclusionary:
        i. A positive result for antiphospholipid antibodies at screening is not exclusionary provided there is no history of thrombosis or pregnancy mortality
        ii. A thrombotic event more than 12 months before screening is not exclusionary provided the subject is maintained on appropriate anticoagulation therapy (warfarin, low-molecular weight heparin, or newer anticoagulants)
        iii. A history of APS with a history of pregnancy morbidity more than 12 months before screening is not exclusionary provided the subject is maintained on low-dose aspirin or equivalent
i. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by British Isles Lupus Assessment Group (BILAG) A criteria, with the exception of subjects with mononeuritis multiplex and polyneuropathy, which are allowed with the approval of CRS.
j. N/A per Revised Protocol 6

k. Dialysis within 12 months before screening or plans for dialysis after enrollment in the study

2) Other Medical Conditions and History

a. Women who are pregnant or breastfeeding
b. Screening systolic blood pressure > 150 and/or diastolic blood pressure > 90 mmHg (based on the average of two readings at least 5 minutes apart); if the systolic blood pressure is 150 mmHg to 170 mmHg and/or diastolic pressure is 90 mmHg to 100 mmHg at screening, the subject must be managed during Part A of the study so the blood pressure is no higher than 150/90 mmHg at the time of randomization (based on the average of two readings taken at least 5 minutes apart)
c. Body mass index (BMI) ≥ 40 kg/m^2 at screening
d. Any major illness/condition, evidence of an unstable clinical condition, or symptoms of a severe, progressive, or uncontrolled condition (eg, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, psychiatric, or non-SLE-related renal disease) or local active infection/infectious illness that, in medical judgment, might place the subject at unacceptable risk for participation in this study
e. Any major surgery within 30 days before the first dose of study treatment or any surgery planned during the course of the study
f. Cancer or history of cancer or lymphoproliferative disease within 5 years before screening (other than successfully treated cutaneous basal cell or squamous cell carcinoma or cervical carcinoma in situ with no evidence of recurrence within 1 year before the screening visit)
g. New York Heart Association (NYHA) Class III or IV congestive heart failure or any recent onset of heart failure resulting in NYHA Class III/IV symptoms
h. Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before screening
i. Serious thrombotic event(s) (eg, pulmonary embolism, stroke, deep vein thrombosis) within 1 year before the screening visit
j. Current or recent (within 3 months before randomization) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of oral study treatment
k. Non-SLE concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study (eg, asthma)
l. Severe, progressive, or uncontrolled kidney, liver, blood, stomach, lung, heart, or brain disease not due to active SLE
m. Comorbid conditions requiring systemic corticosteroid use in the 52 weeks before screening (topical or inhaled corticosteroids are not exclusionary)
n. Poorly controlled or advanced diabetes mellitus, as evidenced by a hemoglobin A1c of ≥ 8.0% at screening, or by active diabetic complications such as diabetic nephropathy
o. Evidence of a degree of tubulointerstitial changes that suggest a significant and irreversible decrease in renal function (> 50% tubulointerstitial fibrosis or > 50% glomerulosclerosis)

p. Renal disease unrelated to SLE including persistent, non-SLE-related pyuria or hematuria (eg, hemorrhagic cystitis)
q. Significant blood loss (> 500 mL) or blood transfusion within 4 weeks before randomization
r. Inability to tolerate oral medication
s. Inability to tolerate venipuncture and/or inadequate venous access
t. Recent (within 6 months before screening) substance dependence or abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders IV (see APPENDIX 8)
u. Any disease or medical condition that, based on medical opinion, would make the subject unsuitable for this study, would interfere with the interpretation of subject safety or study results, or considered unsuitable by the investigator for any other reason

3) Prior and Concomitant Therapy

a. N/A per Revised Protocol 10
b. Inability to comply with restrictions and prohibited treatments listed in Section 6.10.1
c. Previous exposure to TYK2 or JAK inhibitors
d. Previous exposure to anifrolumab, ustekinumab, or interferon-α kinoid vaccines
e. Administration of rituximab within 52 weeks before screening
f. Administration of cyclophosphamide or IV immunoglobulin within 24 weeks before screening
g. A history of plasmapheresis within 24 weeks before screening
h. Administration of oral or IV calcineurin inhibitors (eg, cyclosporine, voclosporin, tacrolimus) within 4 weeks before screening
i. Current administration of opioids unless all the following criteria are met:
    a. The prescribed dose has been stable for at least 2 weeks before randomization
    b. N/A per Revised Protocol 6
    c. N/A per Revised Protocol 6
    d. In the opinion of the investigator, the subject's use of opioids will not impact the protocol-specific efficacy and safety assessments
    e. The dose does not exceed the equivalent of 30 mg of morphine per day (see APPENDIX 15 for morphine milligram equivalents of commonly used opioids)
j. Any current or anticipated use of nonsteroidal anti-inflammatory drugs unless approved by the [redacted] medical monitor (aspirin is allowed at stable doses no higher than 325 mg/day throughout the study)
k. Other investigational agents must be discontinued at least 12 weeks or 5 half-lives before screening, whichever is longer
l. Use of concomitant medications known to interact with MMF
m. Current administration of immunosuppressants other than MMF, aminoquinolines (eg, hydroxychloroquine), or corticosteroids; see APPENDIX 7 for required discontinuation times for specific drugs; exceptions must be discussed with and approved by the medical monitor. (If previously treated with MMF and subsequently discontinued, there must have been at least a 6-month washout period before restarting MMF in Part A; it is acceptable for subjects to have been on ≤ 750 mg/day MMF chronically, provided the

MMF is ongoing at screening; subjects on > 750 mg/day at the time of screening may not have been on the higher dose for more than 24 weeks prior to screening)

4) Findings Related to Possible Infection

a. Evidence of active or latent tuberculosis (TB) as follows:
   i. History of active TB, regardless of completion of adequate treatment
   ii. Current signs or symptoms of active TB during screening as judged by the investigator
   iii. Documentation of a chest x-ray obtained during screening (or results of an X-ray or computed tomographic [CT] scan of the chest within 6 months before screening) with evidence of current active or old active pulmonary TB
   iv. Latent TB infection (LTBI), defined as a positive IFN-gamma release assay (IGRA) by QuantiFERON®-TB Gold, QuantiFERON®-TB Gold Plus, or T-Spot® testing at screening, or other diagnostic test, in the absence of clinical manifestations; **Note:** such subjects may be eligible if (1) there are no current signs or symptoms of active TB and (2) the subject has received adequate documented treatment for LTBI within 5 years of screening OR has initiated prophylactic treatment for LTBI per local guidelines and is rescreened now after 1 month of treatment. The subject must agree to complete a locally recommended course of treatment for LTBI to continue in the study
   v. N/A per Revised Protocol 10
   vi. An indeterminate IGRA result at screening with no signs or symptoms of active TB; **Note:** A subject with an indeterminate IGRA test result at screening must be retested for confirmation. If approved by the [redacted] medical monitor, the repeat test may be performed locally and may be a different type of IGRA assay. If the second result is again indeterminate, the TB questionnaire (APPENDIX 20) will be completed. If the TB questionnaire indicates no new/recent risks, then the subject may be eligible provided no other exclusion criterion for TB is met and ongoing IGRA testing will occur every 6 months per Section 8.7.2. If there are new/recent risks, the subject will be excluded from the study. If the second result is positive, the subject should be treated as having LTBI. If the second result is negative, the subject may be eligible provided no other exclusion criterion for TB is met.

b. Any of the following hepatitis B (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) serology results at screening:
   i. Evidence of HBV, defined as any of the following:
      i. Positive hepatitis B surface antigen (HBsAg)
      ii. Presence of HBV deoxyribonucleic acid (DNA)
      iii. Positive for anti-hepatitis B core antibody (anti-HBc) without concurrent positive hepatitis B surface antibody (anti-HBs)

ii. Evidence of HCV, defined as both of the following:

i. positive for antibodies to HCV

ii. positive result for confirmatory test for HCV (polymerase chain reaction)

iii. Positive for antibodies to HIV-1 or HIV-2

c. Currently receiving therapy for chronic infection (eg, pneumocystis, cytomegalovirus, herpes simplex, herpes zoster, invasive bacterial or fungal infections, or atypical mycobacteria); medications used for prophylaxis are not exclusionary

d. History of congenital or acquired immunodeficiency

e. Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (intramuscular or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days before randomization, or completion of oral antimicrobial agents within 2 weeks before randomization

f. Administration of a live vaccine or inactivated vaccine within 30 days before screening; influenza and pneumococcal vaccines may be administered at any time but the effect of BMS-986165 on vaccine response is unknown; live vaccines should not be used during treatment or within the 2 months following the last dose of blinded study treatment, and any other inactivated vaccines (eg, tetanus) should be used according to local guidelines during the treatment period

g. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection (either suspected or confirmed) within 12 weeks of screening.

5) Physical Examination and Laboratory Results

a. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, or clinical laboratory determination beyond what is consistent with the target population

b. Clinically significant abnormalities on screening chest x-ray or electrocardiogram (ECG) unless due to SLE

c. Clinically significant abnormalities in screening laboratory results, including:

i. Positive direct antiglobulin test (Coombs test) and evidence of hemolysis

ii. Serum alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN), unless explicitly related to SLE

iii. Serum aspartate aminotransferase (AST) > 2 × ULN, unless explicitly related to SLE

iv. Serum total bilirubin > 1.5 × ULN, unless explicitly related to SLE or documented Gilbert's syndrome

v. Hemoglobin < 8 g/dL (80 g/L)

vi. eGFR (using the MDRD equation) ≤ 30 mL/min/1.73 m^2

vii. Absolute neutrophil count (ANC) < 1.2 × 10^3/µL (1.2 × 10^9/L)

viii. Platelet count < 50 × 10^3/µL (50 × 10^9/L)

d. Abnormal free T4: if a subject has an abnormal TSH at screening (relative to the laboratory reference range), free T4 will be assessed. Those with abnormal free T4 will be excluded unless they have a prior diagnosis of a thyroid disorder and are currently receiving thyroid replacement therapy; these subjects may rescreen after a minimum of 6 weeks after adjustment of thyroid hormone replacement therapy. Such cases should be discussed with the [redacted] medical monitor. Any other significant laboratory or other abnormalities that, in the opinion of the investigator, might pose an unacceptable risk to the subject during the study

6) Allergies and Adverse Drug Reaction

a. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)

7) Other Exclusion Criteria

a. Involuntary incarceration such as imprisonment (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and BMS approval is required)
b. Compulsory detention for treatment of psychiatric or physical illness (eg, infectious disease)
c. Inability to comply with the study protocol

5.3 Lifestyle Restrictions

No restrictions are required. However, general skin care measures are recommended that are standard for patients with SLE, as follows: use of broad spectrum sunscreen (minimum sun protection factor 15 and with inorganic ingredients [zinc oxide, titanium dioxide]), avoiding sun exposure, wearing sun-protective clothing, avoiding alcohol-based emollients, over-the-counter anti-acne medications, alcohol-based skin care products, and perfumed soaps and detergents, and similar measures.

5.3.1 Meals and Dietary Restrictions

The blinded study treatment may be taken without regard to meals; however, subjects are required to fast for a minimum of 10 hours before visits at which blood samples will be collected for the fasting lipid profiles [redacted].

5.3.2 Caffeine, Alcohol, and Tobacco

There are no study-specific restrictions on caffeine, alcohol, or tobacco use.

5.3.3 Activity

There are no restrictions on physical activity.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet the study eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory

authorities. Minimal information includes date of consent, demographic data, screen failure details, eligibility criteria, and any serious AEs (SAEs).

5.4.1 Retesting During the Screening Period

The study permits the re-enrollment of a subject who discontinues the study as a pretreatment failure (ie, the subject fails screening and has not been treated), with the approval of the [redacted] medical monitor. If re-enrolled, the subject must sign a new informed consent form (ICF). In some instances, investigators may rescreen a subject more than once after discussion with and approval of the medical monitor.

Laboratory parameters and/or assessments that are included in Table 1 may be repeated one time in an effort to find all possible well-qualified subjects. Consultation with the [redacted] medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

The most current result will be used to assess eligibility for study inclusion because it represents the subject's most current clinical state.

If a subject is rescreened, the same parameters regarding the time since renal biopsy and chest x-ray, and time on MMF therapy will apply.

6 TREATMENT

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study subject according to the study randomization or treatment allocation.

An IP, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventive, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered to be non-IPs. Table 5 shows the treatments for this study.

Table 5: Study Treatments for Protocol IM011073

Product Description/ Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986165 oral tablet	3 mg or 6 mg	IP	Blinded	Blister card containing 64 tablets	Store at 15°to 25°C. Store in original container. Protect from light.
Placebo matching BMS-986165 oral tablet	N/A	IP	Blinded	Blister card containing 64 placebo tablets	Store at 15°to 25°C. Store in original container. Protect from light.
Mycophenolate mofetil	500 mg	IP	Open label	Bottles or blister card of tablets	See storage conditions on the container

IP = investigational product

6.1 Mycophenolate Mofetil Target Dose and Dose Modification

For subjects who will be starting MMF in Part A, treatment will be initiated at 500 mg BID. If tolerated, the dose will be increased to a suggested target dose of 1.5 to 2.0 g/day (subjects self-described as Asian) or 2.0 g/day (all others) one week after initiating MMF. Subjects who have been on MMF at a dose of ≤ 750 mg/day at the time of screening will follow the same escalation schedule as those starting MMF. For subjects self-described as Black, African American, or of African descent, the dose will be further increased to 3.0 g/day two weeks after initiating MMF. The following suggested target doses of MMF should be reached by the time of randomization:

- 1.5 to 2.0 g/day for subjects self-described as Asian or of Asian descent
- 3.0 g/day for subjects self-described as Black, African American, or of African descent
- 2.0 g/day for all others, with the following exception:

Subjects entering the study on a stable dose of MMF greater than the target may continue that dose if it is no greater than 3.0 g/day. In some non-African subjects, the investigator may believe that it is in the best interest of the subject to use doses higher than 2.0 g/day; this is allowed provided the dose is not higher than the maximum of 3.0 g/day.

From Week 6 of MMF treatment in Part A through the end of Part B, the MMF dose should remain stable with the following exceptions:

- A change from a BID to a three times daily (TID) regimen is permitted as long as the total daily dose remains unchanged
- Per the MMF prescribing information, if neutropenia develops (ANC < 1300/μL), MMF dosing should be interrupted or the dose reduced, appropriate diagnostic tests should be performed, and the subject should be managed appropriately.

After a subject reaches the target dose, the dose should remain stable through the end of Part B; however, if necessary because of intolerance, the rate of dose increase may be slowed, or the dose may be divided and administered TID, at the discretion of the investigator.

If a subject cannot tolerate the MMF dose or the investigator has concerns about over-immunosuppression, the target dose may be reduced; however, subjects unable to tolerate a minimum dose of 1.5 g/day in Part A should be discontinued from study treatment and will be considered enrollment failures.

Women of childbearing potential who are starting MMF in Part A must have a negative urine pregnancy test within 24 hours before the first dose, and per the MMF prescribing information, these subjects should also have another urine pregnancy test between 8 and 10 days after the first dose. For the subjects' convenience, this second pregnancy test may be performed at a local laboratory; the site staff should call subjects to whom this requirement applies and remind them to obtain the test at the investigative site or a local laboratory.

6.2 Laboratory Monitoring for Mycophenolate Mofetil Toxicity

In accordance with the prescribing information, subjects should have a complete blood count (CBC) performed weekly for the first month of MMF therapy, twice monthly for the second and third month, and then monthly thereafter for the first year of therapy. If these monitoring CBCs coincide with scheduled study visits, the central laboratory results for that visit may be used; if any of these CBCs are needed in between scheduled study visits, these may be performed at a local laboratory. The site staff should contact subjects to whom this monitoring applies and remind them to obtain the test either at the investigative site or a local laboratory.

For those subjects already taking MMF before signing the ICF, it is expected that the investigator will manage safety monitoring per the standard of care and in accordance with the MMF prescribing information.

6.3 Treatments Administered

6.3.1 Open-label Mycophenolate Mofetil – All Subjects

Open-label MMF will be dispensed to all subjects in Part A, Part B [redacted].

6.3.2 Blinded Study Treatment in Part B – Randomized Subjects Only

Blinded study treatment in Part B will be supplied in blister card kits. The tablets will be arranged into sets to be taken in the morning and in the evening, approximately 12 hours apart. If a subject forgets a dose of blinded study treatment, but remembers within 4 hours of the expected dose, the dose should be taken. If the missed dose is discovered more than 4 hours after it should have been taken, that dose should be not be taken and the next scheduled dose should be taken at the usual time. Any missed doses should be returned at the next study visit.

Table 6 shows the blinded study treatments in Part B.

Table 6: Selection and Timing of Blinded Study Treatment Dosing

Treatment Group	Unit dose strength	Dosage formulation Frequency of Administration	Route of Administration
3 mg BID BMS-986165	3 mg	1 active and 1 placebo tablet in the morning and 1 active and 1 placebo tablet in the evening	Oral
6 mg BID BMS-986165	6 mg	1 active and 1 placebo tablet in the morning and 1 active and 1 placebo tablet in the evening	Oral
Placebo BID	N/A	2 placebo tablets in the morning and 2 placebo tablets in the evening	Oral

BID = twice daily

[redacted]

6.4 Subject Number Assignment

At the screening visit, before any study-related procedures are performed, the investigative site will access the interactive response technology (IRT) for assignment of the subject number. This number will be assigned sequentially by the system and will be unique across all sites. If a potential subject is rescreened, they will be given a new identification number.

6.5 Blinding – Part B [redacted]

At Visit B1, subjects who meet the criteria to continue in Part B and meet the randomization criteria will be centrally randomized using IRT to receive BMS-986165 3 mg BID, BMS-986165 6 mg BID, or placebo BID. These criteria are listed in Section 4.1.2.1 and 4.1.2.2, respectively.

[redacted]

All blinded study treatments will be supplied in blister packs with each daily dose made up of active or placebo tablets. The investigative site staff, Sponsor and designated personnel, and subjects and their families will remain blinded to treatment assignments through the end of Part B.

This study will be conducted as a double-blind study for the placebo-controlled treatment period (Part B). [redacted]

For the Week 24 database lock (primary efficacy endpoint), personnel who have access to the unblinded data are not to discuss or make materials available that would unblind individual subjects' data to the personnel involved in the study conduct. Access to treatment codes will be restricted from all participants and site personnel prior to final database lock, with exceptions as specified below.

Blinding of randomized treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the blinded study treatment is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded. In case of an emergency, the investigator has unrestricted access to randomization information and may break the blind through the IRT system without prior approval from the Sponsor. Following the unblinding, the investigator shall notify the [redacted] medical monitor.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the blinded study treatment, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the [redacted] medical monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should call in for emergency unblinding only after the decision to discontinue the subject has been made.

In cases of accidental unblinding, the investigator must contact the [redacted] medical monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for nonemergency purposes should be discussed with the [redacted] medical monitor.

6.6 Dosage Modification

There is no provision for modification of the dose of blinded study treatment.

Corticosteroid tapering is discussed in Section 6.6.1.

See Section 6.1 for information about MMF dose modification.

6.6.1 Corticosteroid Tapering and Corticosteroid Rescue in Part B [redacted]

Corticosteroids are permitted but not required in this study. One of the criteria to continue in the study during Part B is that the corticosteroid dose (if any) must not exceed 25 mg/day of prednisone or prednisone equivalent. Management of corticosteroids including initiation and dosing in Part A will be at the discretion of the investigator. All corticosteroid doses in this section of the protocol refer to prednisone. See APPENDIX 6 for prednisone-equivalent doses of other corticosteroids.

For subjects deemed by the investigator to be appropriate for corticosteroid tapering, this section includes a guideline and a suggested sequence of tapering.

Subjects will be assessed for SLE flare at study visits every 4 weeks throughout Part B. Flare assessments will be made in comparison to the previous visit. Corticosteroid doses may be tapered at the time of a study visit, and at the investigator's discretion, subjects may be instructed to adjust the corticosteroid dose in between study visits. For example, at a study visit, an investigator may taper the dose and instruct a subject to taper again to the next lower dose (to be specified) 2 weeks later if they are feeling well. Likewise, after a study visit at which the dose is tapered, an investigator may instruct the subject to resume the previous dose before the next study visit if needed because of intolerance.

Subjects who respond to MMF during Part A and therefore do not meet the randomization criteria, but who continue open-label MMF in Part B will follow the same corticosteroid taper.

Randomized subjects taking corticosteroids will be required to have their dose tapered during Part B unless there is evidence of increased extrarenal disease activity as assessed by the rSFI (clinical component only; the renal system will not be assessed with the rSFI; see APPENDIX 17) or worsening or unstable renal findings per the OSS Flare Index (see APPENDIX 16) as follows:

- If either flare index indicates a moderate or severe flare, the corticosteroid dose should not be tapered
- If either flare index indicates a mild flare, or if there is no flare but there is another reason not to taper the corticosteroid dose, the investigator must contact CRS, which will refer the case to the study-designated nephrology or rheumatology Therapeutic Expert for additional review

Unless they have a moderate or severe flare as defined above, randomized subjects will have their corticosteroid dose tapered as follows:

- Corticosteroid dose tapering should start by Week 4 in Part B

- After the dose is tapered to the lower dose level, subjects should remain on the new corticosteroid dose for at least 2 weeks before further tapering
- The goal for corticosteroid tapering is to reduce the dose to 7.5 mg/day prednisone or equivalent by Week 24; the dose may continue to be tapered below 7.5 mg/day at the investigator's discretion
- Subjects on a baseline dose of 25 mg/day of prednisone or equivalent will have their dose tapered by 5 mg to 20 mg/day; thereafter, the dose will be tapered by 2.5-mg increments until they reach 7.5 mg/day (tapering may continue at the discretion of the investigator)
- Subjects on a baseline dose of ≤ 20 mg/day of prednisone or equivalent will have their dose tapered by 2.5-mg increments until they reach 7.5 mg/day (tapering may continue at the discretion of the investigator)
- No dose tapering will occur during the 4 weeks leading up to the visit at Week 24 and at Week 52, to allow 4 weeks of stable dosing before the efficacy assessments at these visits; in other words, the dose may be tapered at Week 20, but then should remain stable until the efficacy assessments at Week 24; similarly, the dose may be tapered at Week 48, but then should remain stable until the efficacy assessments at Week 52
- During the course of corticosteroid dose tapering, resumption of the previous dose (one dose level higher than the current dose) is allowed, but resumption of a dose higher than the previous dose (more than one dose level higher than the current dose) is not allowed, except for the following:
    - During the first 8 weeks in Part B, a single corticosteroid burst of up to 40 mg/day prednisone or equivalent is allowed, but the dose must be tapered back to the previous dose within 2 weeks after initiating the burst
- [redacted]

In the following situations, subjects may continue to receive blinded study treatment in Part B but will be considered nonresponders for analysis purposes:

- The corticosteroid burst dose cannot subsequently be tapered within 2 weeks of initiating the burst
- More than a single corticosteroid burst is needed
- A corticosteroid burst is needed after Week 8
- There is a need to increase the dose by more than one dose level higher than the current dose

Table 8 shows the recommended sequence of corticosteroid dose reductions that should be followed for all subjects, according to the dose at the time of randomization, but the actual frequency of tapering and duration of time at each tapered dose may vary between subjects and will be determined by the investigator.

Table 8: Corticosteroid Dose Tapering Sequence by Dose at Randomization (Visit B1)

	Prednisone or Equivalent Dose (mg/day) at Randomization								
Sequence	**25**	**20**	**17.5**	**15**	**12.5**	**10**	**7.5**	**5**	**2.5**
Taper 1	20	17.5	15	12.5	10	7.5	5	2.5	0
Taper 2	17.5	15	12.5	10	7.5	5	2.5	0	
Taper 3	15	12.5	10	7.5	5	2.5	0		
Taper 4	12.5	10	7.5	5	2.5	0			
Taper 5	10	7.5	5	2.5	0				
Taper 6	7.5	5	2.5	0					
Taper 7	5	2.5	0						
Taper 8	2.5	0							
Taper 9	0								

6.7 Treatment After the End of the Study

At the end of the study, the investigator should encourage subjects to continue appropriate standard medical care for SLE and LN.

In addition, for subjects who continue to demonstrate clinical benefit, BMS may elect to continue to provide study treatment via an extension of the current study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur:

a. The study is terminated due to safety concerns or other reasons, including but not limited to lack of efficacy and/or failure to meet study objectives

b. Development of BMS-986165 for the treatment of LN and/or the development of the compound is terminated for other reasons, including but not limited to lack of efficacy and/or failure to meet study objectives

c. The subject can obtain medication from a government-sponsored or private health program; in all cases, BMS will follow local regulations

6.8 Preparation/Handling/Storage/Accountability

All IP (MMF and blinded study treatment) should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is dispensed only to study subjects. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that all study treatments are stored in accordance with the environmental conditions (temperature, light, or humidity) as determined by BMS. If concerns regarding the quality or appearance of the blinded IP arise, the study treatment should not be dispensed and the investigator should contact BMS immediately.

Study-supplied MMF should be stored according to the instructions on the packaging.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether the IP is supplied by BMS or not) must be maintained and must include all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets). Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 2.

6.8.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable

6.9 Treatment Compliance

Compliance with MMF and blinded study treatment will be monitored using standard drug accountability procedures such as comparing the number of tablets returned to the number dispensed, according to the expected regimen and any reported missed doses. Subjects should be instructed to bring all unused MMF and blinded IP to each study visit. Drug accountability will be reviewed by the investigative site staff at each visit to confirm treatment compliance. Site staff will discuss any discrepancies and remind the subject of the importance of compliance with the assigned regimen. A real-time monitoring platform may be used.

Several times during the study, compliance with MMF therapy will be assessed by measuring the trough MPA concentration.

6.10 Previous and Concomitant Therapy

All previous medications for SLE will be recorded.

All medications (including MMF obtained outside the study) taken within 4 weeks before the first dose of study-supplied MMF in Part A through the final study visit must be recorded on the concomitant medication electronic case report form (eCRF). The only exception is that corticosteroids must be recorded on the Corticosteroid Dose Log starting at Visit B1.

Corticosteroid dosage and tapering guidelines are discussed in Section 6.6.1.

Changes in dosing of SLE medications in the 12 weeks before screening should be recorded, but with regard to dosing changes more than 12 weeks before screening, just the final dose of the medication with inclusive dates should be recorded.

Other than existing allowed concomitant treatment for SLE or LN, other prescription or over-the-counter medications should be administered only if they are prescribed for the treatment of specific clinical events.

6.10.1 Prohibited and/or Restricted Treatments in Part A and Part B

Prohibited and/or restricted medications during Part A and Part B are listed below:

1. Administration of opioids unless all the following criteria are met:
    a. The prescribed dose has been stable for at least 2 weeks before randomization
    b. In the opinion of the investigator, the subject's use of opioids will not impact the protocol-specific efficacy and safety assessments
    c. The dose does not exceed the equivalent of 30 mg of morphine per day (see APPENDIX 15 for morphine milligram equivalents of commonly used opioids)
2. Any use of nonsteroidal anti-inflammatory drugs unless approved by the [redacted] medical monitor (aspirin is allowed at stable doses no higher than 325 mg/day throughout the study)
3. Lymphocyte apheresis or selective monocyte, granulocyte apheresis (eg, Cellsorba®)
4. Live vaccines during the study or within 2 months after the last dose. Heat-killed (or otherwise inactivated) or protein vaccines such as influenza and pneumococcal vaccines may be received at any time during the study. Any other inactivated vaccines such as tetanus should be used according to local guidelines
5. Immunosuppressants other than MMF, aminoquinolines (eg, hydroxychloroquine), or corticosteroids
6. Use of cyclophosphamide (including ophthalmic), any biologic agent, or other medications listed in APPENDIX 7
7. Anifrolumab, ustekinumab, or interferon-α kinoid vaccines
8. Exposure to any investigational agent or placebo outside the current study
9. Rescue therapy other than prednisone or equivalent (APPENDIX 6)
10. Modified-release corticosteroid formulations
11. Concomitant medications known to interact with MMF
12. Any other drugs, including over-the-counter medications and herbal preparations except those approved by the [redacted] medical monitor

6.10.2 Permitted Concomitant Medications in Part A and Part B

Stable doses of concomitant medication for chronic medical conditions that are not listed in the exclusion criteria (Section 5.2) or the prohibited and/or restricted treatments (Section 6.10.1) are permitted in Part A and Part B if approved by the [redacted] medical monitor. Dose adjustments of these medications should be avoided during the study unless clinically indicated. If a dose adjustment of these medications should occur, they must be recorded on the Concomitant Medications eCRF or the Diagnostic and Medical Procedures eCRF. The investigator should instruct the subject to notify the study site about any new treatments he or she takes after the start of the study treatment. All medications and significant nondrug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be listed on the Concomitant Medications eCRF or the Diagnostic and Medical Procedures eCRF.

7 DISCONTINUATION CRITERIA

7.1 Discontinuation from Study Treatment

Subjects MUST discontinue the IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- A subject requests to stop study treatment; these subjects will remain in the study and must continue to be followed for protocol-specified follow-up procedures, unless the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study or the program by BMS
- Loss of ability to provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

In the case of pregnancy, all study treatment must be stopped immediately. The investigator must immediately notify the [redacted] medical monitor or designee of this event (no later than 24 hours after becoming aware of the pregnancy). See Section 8.5.6 for more information about pregnancy.

Unless they withdraw consent for further follow-up procedures or lose the ability to consent freely (eg, through imprisonment or involuntary incarceration for treatment of psychiatric or physical illness), subjects who discontinue from the study treatment early should still attend the final

end-of-treatment visit and the 28-day follow-up visit. They will also be followed for SAEs for 30 days after the final dose of IP, and will be evaluated on a case-by-case basis regarding the optional end-of-treatment renal biopsy.

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate eCRF page.

7.2 Week 24 Subject Status Evaluation

At Week 24 (Visit B7), investigators should assess, based on their clinical judgment, if continuation in the study remains in the subject's best interest, overall and with regard to progression of renal disease. If the investigator determines that continuation is no longer in a subject's best interest, the subject should stop the study treatment immediately, but if possible, should remain in the study for appropriate follow-up procedures as outlined in Sections 7.3 and 7.4. The investigator will record the reason for discontinuation and will report any AEs or SAEs (see Section 8.5 and APPENDIX 3).

7.3 Discontinuation from the Study

Unless they withdraw consent for further follow-up procedures or lose the ability to freely consent (eg, through imprisonment or involuntary incarceration for treatment of psychiatric or physical illness) subjects who discontinue from the study early should still attend the 28-day follow-up visit. They will also be followed for SAEs for 30 days after the final dose of IP.

Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.

The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page.

In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.4 Follow-Up After Early Discontinuation from Study Treatment

In this study, renal response is a key endpoint of the study. Follow-up procedures are of critical importance and are essential to ensuring subject safety and the integrity of the study. Investigators should continue to follow subjects who are discontinued early from the study treatment, for collection of outcome data for 30 days after the final dose of the study treatment, or until death or the conclusion of the study, as required, unless subjects withdraw consent for further follow-up.

7.5 Lost to Follow-Up

Investigative site staff must make reasonable efforts to locate study subjects to determine and report their ongoing status. These efforts include follow-up with persons authorized by the subject to provide information.

A subject will be considered lost to follow-up if there is no response to a minimum of 3 documented phone calls, faxes, or emails, and a registered letter. The site staff will document all attempts at communication in the subject's medical records.

If it is determined that the subject has died, the site will use permissible local methods to obtain date and cause of death.

If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist the site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study.

The site staff and representatives will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.

If after all attempts, the subject remains lost to follow-up, then the last date the subject was known to be alive should be reported and documented in the subject's medical records.

8 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures are summarized in the Schedules of Activities (see Section 1.3).

Protocol waivers or exemptions are not allowed.

All immediate safety concerns must be discussed with the [redacted] medical monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

Adherence to the study design requirements, including those specified in the Schedules of Activities, is essential and required for study conduct.

Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Part A Assessments

Assessments during Part A will be conducted for safety monitoring, [redacted] and at Visit A4, evaluation of the criteria to continue in Part B and for randomization.

Women of childbearing potential must have a negative urine pregnancy test within 24 hours of the first dose (or first on-study dose) of MMF, and at each study visit in Part A. Women of childbearing potential who are beginning treatment with MMF in Part A must also have another urine pregnancy test between 8 and 10 days after the first dose of MMF; this test may be performed at a local laboratory, and the site staff will contact the subjects to whom this requirement applies, and remind them to obtain the test either at the investigative site or a local laboratory.

Per the MMF prescribing information, subjects starting MMF in Part A must also have a CBC weekly for the first month, every 2 weeks during the second and third months, and monthly thereafter for the first year of treatment. If the timing of these monitoring CBCs coincides with scheduled study visits, the central laboratory results may be used; if needed in between scheduled study visits, these CBCs may be performed at a local laboratory. Site staff should call subjects to whom this monitoring applies, and remind them to obtain the test either at the investigative site or at a local laboratory.

Most randomization and baseline assessments for Part B will be done at Visit A4, including 24-hour UPCR. Subjects with ≥ 12 weeks but ≤ 24 weeks of MMF treatment at a dose of 1.5 to 3.0 g/day at the time of screening will attend Visit A4 and will collect a 24-hour urine specimen as soon as eligibility is confirmed. For all other subjects, two 24-hour urine specimens will be collected: one approximately 7 to 10 days before Visit A4, and the other just before Visit A4. See Section 8.7.3.2 for details.

Additional regular laboratory assessments in Part A include the following, not including baseline or randomization assessments only at Visit A4 (See Section 8.2):

- Routine chemistry and hematology
- [redacted]
- Trough MPA concentration (at Visit A3; for randomization)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Urinalysis with microscopic examination (and culture if appropriate)
- UPCR on a first morning voided urine sample (or second sample if the first was not collected)

8.2 Part B Assessments

Baseline values may come from assessments at Visit A4 or B1 as indicated in Table 2 and Table 3. All subjects (randomized and nonrandomized) will attend all visits in Part B and will have the assessments listed in Table 3. For premenopausal women, study visits and 24-hour urine collections should be scheduled, when possible, for times when they are not menstruating.

Subjects should be instructed to not take any pain medications for at least 12 hours before their scheduled visits in Part B (except the 28-day follow-up visit [Visit B15]), because these medications may affect some of the assessments.

[redacted]

8.4 Efficacy, Safety [redacted] Assessments

8.4.1 Efficacy Assessments

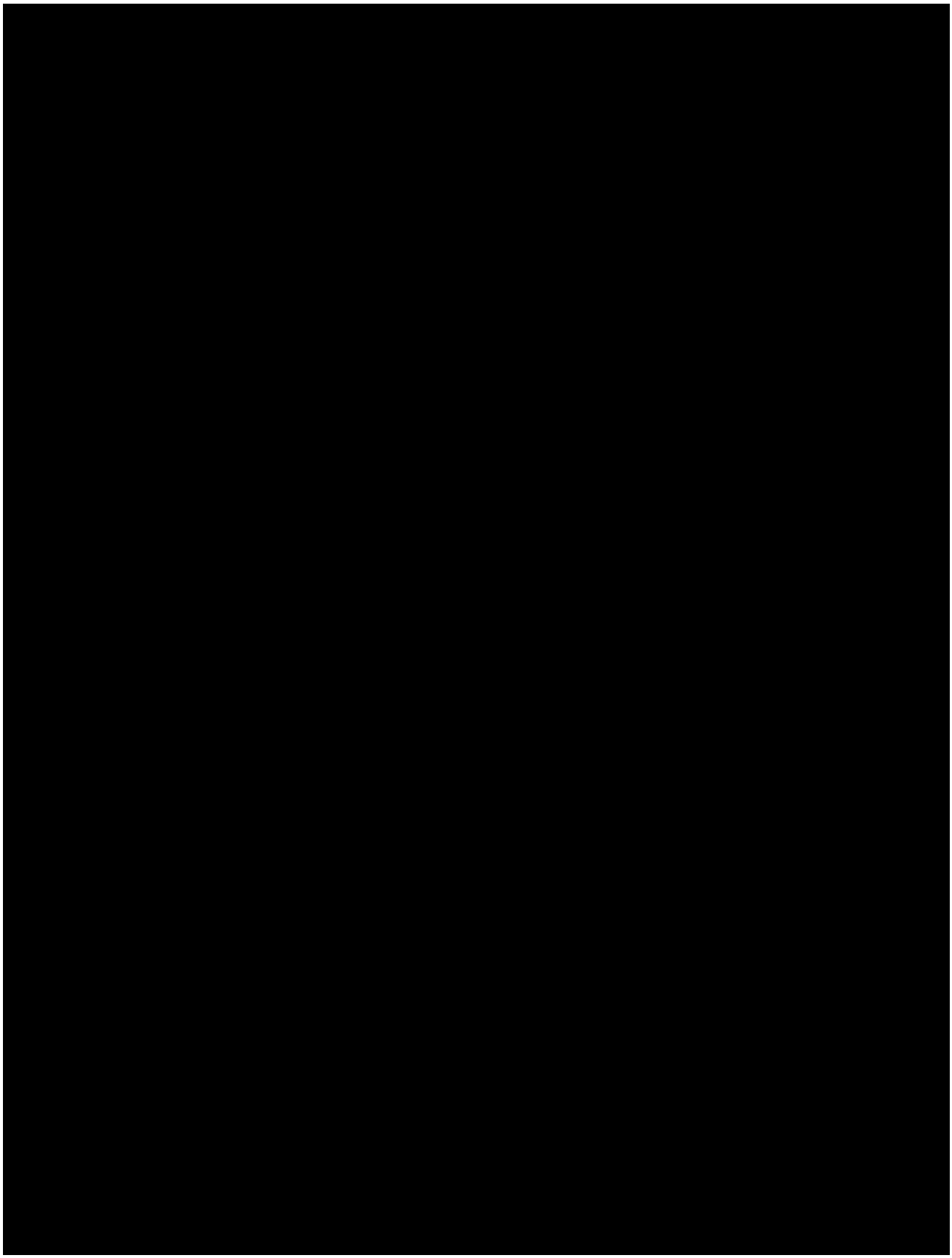
The following assessments will be done during the study (see Section 1.3):

- Laboratory assessments:
  - [redacted]
  - Urinalysis with microscopic examination (clean-catch specimen); if the urinalysis is positive for leukocytes, blood, or bacteria, a urine culture should be performed if appropriate
  - UPCR based on the first morning voided urine specimen (if the first morning voided specimen was not collected, the second morning void will be used)
  - UPCR based on 24-hour urine collections:
    - Two 24-hour urine specimens will be collected for Visits A4 (baseline), B7, and B14 (except for subjects with ≥ 12 weeks of MMF at a dose of 1.5 to 3.0 g/day at the time of screening, who will collect a single 24-hour urine to be compared to their 24-hour UPCR at screening); if the difference in UPCR values between specimens is > 20%, a third 24-hour urine specimen will be collected as soon as possible but no more than 10 days after the results of the results of the first two samples are reported
      - If the third value is within 20% of only one of the previous 2 values, the 2 closest values will be used to compute the average UPCR
      - If the third value is within 20% of both previous values (in the middle), then all 3 values will be used to compute the average UPCR

- If the third value is not within 20% of either of the previous values (all 3 values are > 20% different from each other), then all 3 values will be used to compute the average UPCR
  - [redacted]
- High-sensitivity C-reactive protein (hsCRP)
- Antiphospholipid antibodies (APAs): anticardiolipin antibody (aCL), lupus anticoagulant (LA), and anti-beta-2 glycoprotein-1 (β2GP1) (immunoglobulin [IgA], IgG, and IgM)
- [redacted]
- Antinuclear antibody (ANA)
- [redacted]

- Disease activity and damage indices:
  - [redacted]
  - SLICC/ACR SDI see APPENDIX 10
  - rSFI – clinical component only (excluding the renal system, which is assessed with the OSS Flare Index) see APPENDIX 17
  - OSS Flare Index; see APPENDIX 16

[redacted]



[redacted]

8.5 Adverse Events

The definitions of AEs and SAEs, and contacts for reporting SAEs are in APPENDIX 3.

Adverse events will be reported by the subject or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative.

The investigator and any designees are responsible for detecting, documenting, and reporting AEs and SAEs, and remain responsible for submitting follow-up information on SAEs, study treatment-related AEs, and AEs leading to discontinuation of the study treatment or from the study.

Any AEs or SAEs with a start date and time after the first on-study dose of MMF will be considered treatment-emergent with regard to MMF, and any AEs and SAEs with a start date and time after first dose of blinded study treatment will be considered treatment-emergent with regard to blinded study treatment. Investigators will assess whether the events are related to IP.

8.5.1 Adverse Events of Interest (Part B [redacted])

Adverse events of interest (AEIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AEIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the BMS-986165 clinical development program, certain skin-related AEs (eg, acne) and infection AEs have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with BMS-986165. Therefore, additional information about certain AEs, may be collected on the case report form in order to better characterize and understand them. Therefore, if an AE term corresponding to any of these categories is entered, the user will be prompted by the electronic data capture (EDC) system to enter additional information on the eCRF.

8.5.2 Time Period and Frequency for Collecting Information About Adverse Events and Serious Adverse Events

The collection of nonserious AE information will begin at the first dose of MMF in Part A and will continue until the final study visit. The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB should be used to determine the expectedness of SAEs for expedited reporting.

All SAEs, including those thought to be associated with protocol-specified procedures must be collected from the time the ICF is signed through 30 days after the final dose of any study treatment. Any SAEs that begin after 30 days after the final dose of study treatment must be reported if assessed as related to the study treatment or any protocol-specified procedure.

Medical occurrences that begin after obtaining informed consent but before the first dose of MMF in Part A will be recorded as medical history on the appropriate section of the eCRF module.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours after the investigator or designee becomes aware of the event. The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of learning of the information.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects beyond 30 days after the final dose of any study treatment. However, if the investigator learns of an SAE (including a fatal SAE) after that time and believes the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports is provided in APPENDIX 3.

8.5.3 Method of Detecting Adverse Events and Serious Adverse Events

Adverse events may be spontaneously reported by subjects or may be elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, investigators should avoid asking subjects about specific AE terms.

8.5.4 Follow-up of Adverse Events and Serious Adverse Events

Nonserious AEs should be followed until the event resolves, stabilizes, or is reported as an SAE (see APPENDIX 3).

Follow-up is also required for AEs and SAEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment, as appropriate.

Nonserious AEs must be recorded and described on the nonserious AE page of the eCRF. Completion of supplemental eCRFs may be requested for AEIs such as skin reactions, infections, and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE or SAE report (all subjects), investigators are required to proactively follow each subject at subsequent visits/contacts.

All subjects with SAEs and randomized subjects with AEIs will be followed until the event is resolved or resolved with sequelae, until the condition stabilizes or is otherwise explained, or until the subject is determined to be lost to follow-up (as defined in Section 7.5).

Further information on follow-up procedures is given in APPENDIX 3.

8.5.5 Regulatory Reporting Requirements for Serious Adverse Events

The investigator must promptly report SAEs to the Sponsor so that legal and ethical obligations are met regarding the safety of subjects and the accuracy and completeness of the safety profile of BMS-986165.

If investigators receive SAE reports or other specific safety information (eg, a safety summary or listing of SAEs) from the Sponsor, the site staff will file the documents with the Investigator's Brochure and will notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), if appropriate, according to local requirements.

The Sponsor or designee will be reporting suspected, unexpected serious adverse reactions to the appropriate regulatory authorities and IRBs/IECs according to applicable local and global guidelines and laws, including European Directive 2001/20/EC and Food and Drug Administration Code of Federal Regulations (CFR) 21 Parts 312 and 320.

8.5.6 Pregnancy

In the event a subject becomes pregnant during the trial, the study treatment must be discontinued immediately. If the subject becomes pregnant while on treatment or within 3 days of discontinuing study treatment, the investigator must immediately notify [redacted] Drug Safety of this event and complete and forward a Pregnancy Surveillance Form to [redacted] Drug Safety within 24 hours of awareness of the event in accordance with SAE reporting procedures described in APPENDIX 3. The investigator must also notify the medical monitor or designee of this event within 24 hours of awareness of the pregnancy.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form Investigators will continue to follow-up with subjects who are discontinued from study treatment early because of pregnancy, and will submit additional information on the Pregnancy Surveillance Form regarding the course of the pregnancy, including perinatal and neonatal outcomes.

Any pregnancy that occurs in a female partner of a male subject should be reported to [redacted] Drug Safety. For the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

8.5.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page:

- A laboratory test result that is deemed clinically significant or meets the definition of an AE (if applicable) or SAE
- A laboratory test result abnormality that leads to interruption of or early discontinuation from the blinded study treatment
- A laboratory test result abnormality that requires specific corrective therapy

If a laboratory test result meets the definition of an AE (if applicable) or SAE, the laboratory test result should be reported as an AE or SAE and submitted to [redacted] Drug Safety as specified in APPENDIX 3.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

8.5.8 Potential Drug-induced Liver Injury

Whenever possible, liver-related laboratory abnormalities should be confirmed in a timely manner before a potential drug-induced liver injury (DILI) event is reported. All potential DILIs (defined

as meeting all the criteria below) must be reported as SAEs (see APPENDIX 3 for reporting details):

- Transaminase (ALT or AST) elevation > 3 × ULN
- Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP])
- No other immediately apparent possible causes of AST or ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

8.5.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as an AE or SAE, as appropriate, and reported accordingly.

8.6 Overdose

For this study, any dose of BMS-986165 greater than 24 mg within a 24-hour time period will be considered an overdose. However, if a subject takes a higher dose than assigned (even if less than 24 mg in a 24-hour period), this deviation should be documented appropriately.

In the event of an overdose, the investigator should carry out all of the following actions:

1. Contact the [redacted] medical monitor immediately
2. Closely monitor the subject for AEs, SAEs, and laboratory abnormalities until BMS-986165 can no longer be detected systemically (at least 3 days)
3. [redacted]
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

8.7 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 1.3). All urgent safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment. Only data from protocol-specified procedures and assessments should be submitted on eCRFs. Additional assessments may be performed as part of standard of care, and these data should remain in the subject's medical record but should not be reported on eCRFs.

Safety evaluations in addition to AE monitoring are physical examination (Section 8.7.1), TB screening (Section 8.7.2), vital signs, ECGs, concomitant medication use, and clinical laboratory test results (Section 8.7.3.2).

Planned time points for all safety assessments are listed in the Schedule of Activities.

8.7.1 Physical Examinations

Schedules for physical examinations are provided in Section 1.3. Worsening of lupus or lupus nephritis should be reported in the physical examination as lupus related and on the lupus/lupus nephritis disease assessments.

All physical examinations will be complete examinations and may be performed by a Doctor of Medicine (MD), or someone who is authorized and trained to perform the examinations and has been delegated this task by the Principal Investigator. Although not required, every effort should be made to ensure the same evaluator will complete the examination for each subject at all visits throughout the study. The identity of the examiner is to be recorded in the source notes.

8.7.2 Tuberculosis Screening and Chest Imaging

A physical examination will be performed during screening to assess a subject's eligibility. If available, results of an x-ray or CT scan of the chest from no more than 6 months before screening may be used. Prospective subjects who meet all other eligibility criteria but do not have chest x-ray or CT results within the previous 6 months will need to have a chest x-ray performed as part of screening for TB. A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

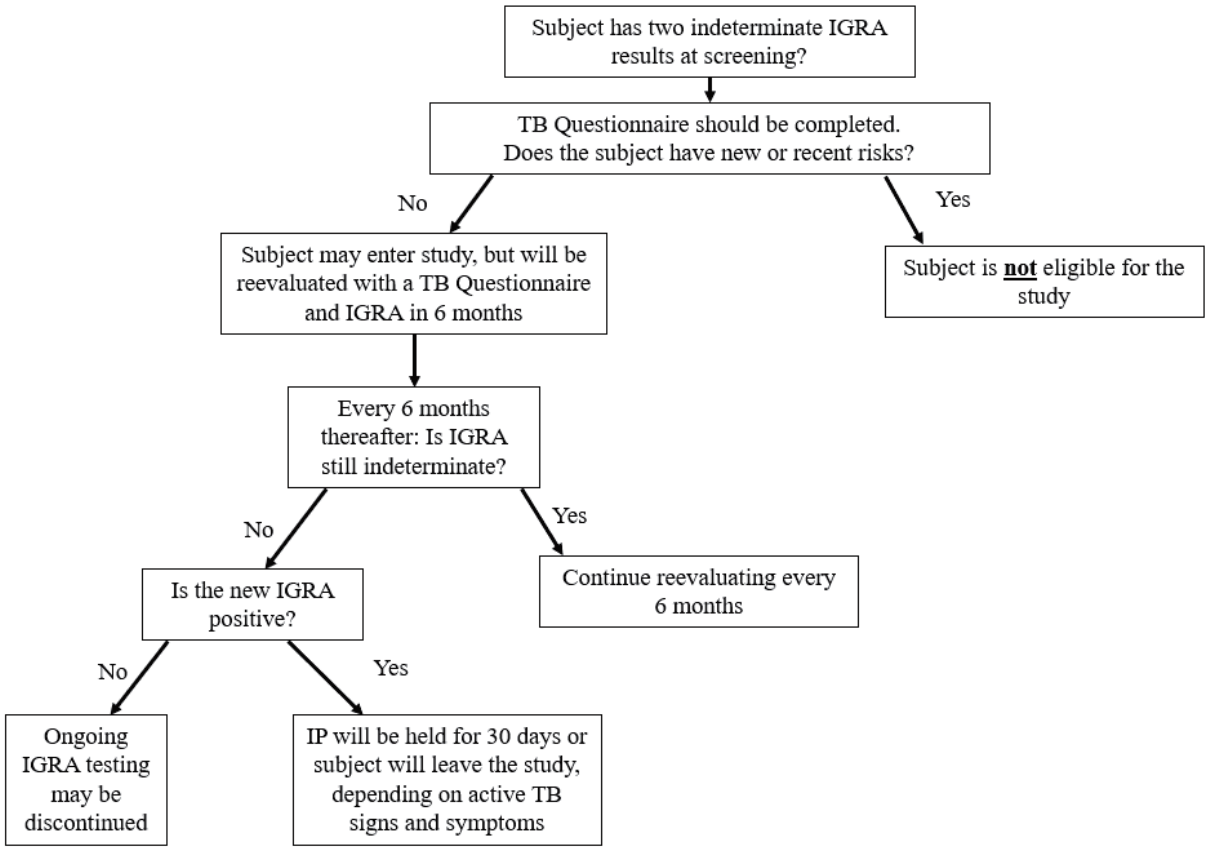
In addition to a complete physical examination and medical history to evaluate exposure to TB, all subjects will have a screening IGRA, eg, T-spot®, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus performed at the central laboratory. A subject with an indeterminate IGRA result at screening must be retested for confirmation; the second test may be performed locally after consultation with the [redacted] medical monitor. If the second result is again indeterminate, the TB questionnaire (APPENDIX 20) will be completed. If this TB questionnaire indicates no new/recent risks, then the subject may be eligible provided no other exclusion criterion for TB is met and ongoing IGRA testing will occur every 6 months. If the TB questionnaire indicates new/recent risks, the subject will be excluded from the study. If the second result is positive, the subject should be treated as having LTBI, provided there are no signs or symptoms of active TB. If the second result is negative, the subject may be eligible to participate in the study, provided no other exclusion criterion for TB is met.

For the subjects with two indeterminate IGRA results at screening who have no new/recent risks per the TB questionnaire, re-evaluation every 6 months with the TB questionnaire and repeat IGRA will be performed:

- If no new risks are identified and IGRA remains indeterminate, continue re-evaluation every 6 months.
- If new risks are identified and IGRA remains indeterminate, investigator will discuss with medical monitor to determine next action based on risks.

- If IGRA is newly negative, then ongoing IGRA testing may be discontinued.
- If IGRA is newly positive, then IP must be held and subject evaluated for active TB. If chest x-ray shows no evidence of active TB and there are no symptoms/signs of active TB, then subject must initiate prophylactic treatment for LTBI per local guidelines. IP will be held until subject has been on prophylaxis treatment for 30 days.

Figure 5: Path for Subjects with Two Indeterminate Interferon-Gamma Release Assay Results at Screening



IGRA = interferon-gamma release assay; TB = tuberculosis

[redacted]

[redacted]

8.7.3 Clinical Safety Laboratory Assessments

The central laboratory will perform safety laboratory assessments (except urine pregnancy tests [redacted]) and provide reference ranges with laboratory reports. Investigators must document their review of each laboratory safety report. A laboratory test result that the investigator considers clinically relevant for safety is to be recorded on the eCRF, if applicable. Results of [redacted] clinical laboratory tests performed during the screening period must be reviewed before the subject is allowed to proceed in the study.

8.7.3.1 Screening Laboratory Assessments

- Chemistry, hematology, coagulation, immunohematology:
    - Metabolic chemistry panel: glucose, blood urea nitrogen (BUN), creatinine (and eGFR using the MDRD equation), sodium, potassium, chloride, carbon dioxide, calcium, phosphate, total protein, albumin, uric acid, total bilirubin, direct bilirubin, phosphorus, magnesium, gamma glutamyltransferase (GGT), ALP, ALT, AST, CK, lactate dehydrogenase (LD), and amylase
    - TSH; if abnormal, a T4 will also be done
    - Follicle-stimulating hormone (FSH) for WOCBP if needed to confirm postmenopausal status (see APPENDIX 4)
    - hsCRP
    - Quantitative immunoglobulins (Igs): IgA, IgG, and IgM
    - Trough MPA concentration (for subjects already taking MMF at screening)
    - CBC: white blood cell (WBC) count, RBC count, hemoglobin, hematocrit, RBC indices, platelet count, and an automated differential; a manual WBC differential will be performed if indicated
    - Coagulation: prothrombin time, International Normalized Ratio, and partial thromboplastin time
    - Direct antiglobulin test (Coombs test) (screening only; thereafter, as needed per investigator)
- Urine:
    - Urinalysis with microscopic examination (if the urinalysis is positive for leukocytes, blood, or bacteria, a urine culture should be performed if appropriate)

  - UPCR assessed using a first morning (or second if the first was not collected) voided urine specimen, and a 24-hour urine specimen
  - Urine pregnancy test (WOCBP only)
- Screening serology: HBsAg, anti-HBs, anti-HBc; HBV DNA if needed; anti-HCV and HCV DNA if needed; anti-HIV-1, anti-HIV-2
- IGRA for TB screening
- ANA
- [redacted]
- APAs: (aCL, LA, and anti-β2GP1)
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

8.7.3.2 Clinical Safety Laboratory Assessments During the Study

A central laboratory will perform safety laboratory assessments (except urine pregnancy tests [redacted]s) and provide reference ranges with the results. Investigators must document their review of each laboratory safety report. Clinically relevant laboratory results (as determined by the investigator) will be recorded on the appropriate AE page of the eCRF (Section 8.5).

See Section 6.1 for information on additional pregnancy testing for WOCBP who initiate the drug in Part A, and Section 6.2 for more information about frequency of CBCs during the first few months of MMF treatment.

Results of clinical laboratory tests performed during screening must be reviewed before the first dose of blinded study treatment. Laboratory assessments for the study include the following:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, RBC indices, platelet count, and an automated differential; a manual WBC differential will be performed if indicated
- Metabolic chemistry panel: glucose, BUN, creatinine (and eGFR using the MDRD equation), sodium, potassium, chloride, carbon dioxide, calcium, phosphate, total protein, albumin, uric acid, total bilirubin, direct bilirubin, phosphorus, magnesium, GGT, ALP, ALT, AST, CK, LD, and amylase
- Urinalysis and microscopic examination of sediment (clean-catch sample); if the urinalysis is positive for leukocytes, blood, or bacteria, a urine culture should be performed if appropriate

- UPCR
  - Visit A4, Visit B7, and Visit B14: Two 24-hour urine specimens will be collected; if a third 24-hour urine specimen is needed, this should be collected as soon as possible but no more than 10 days after the results of the first two specimens are reported; see Section 8.4.1 for more details (the exception is for subjects with 12 weeks of MMF at a dose of 1.5 to 3.0 g/day at the time of screening, who will collect a single 24-hour urine specimen for Visit A4)
  - All visits in Part A, Part B[redacted]: First morning voided urine specimens will be collected; the first morning void is preferred; however, if the first morning void was not collected, the second morning void will be used
  - [redacted]

8.7.4 Body Weight and Vital Signs

Body weight, blood pressure, heart rate, respiratory rate, and temperature will be recorded. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes. At screening, the blood pressure will be measured twice, at least 5 minutes apart, and the average will be used for the eligibility assessment.

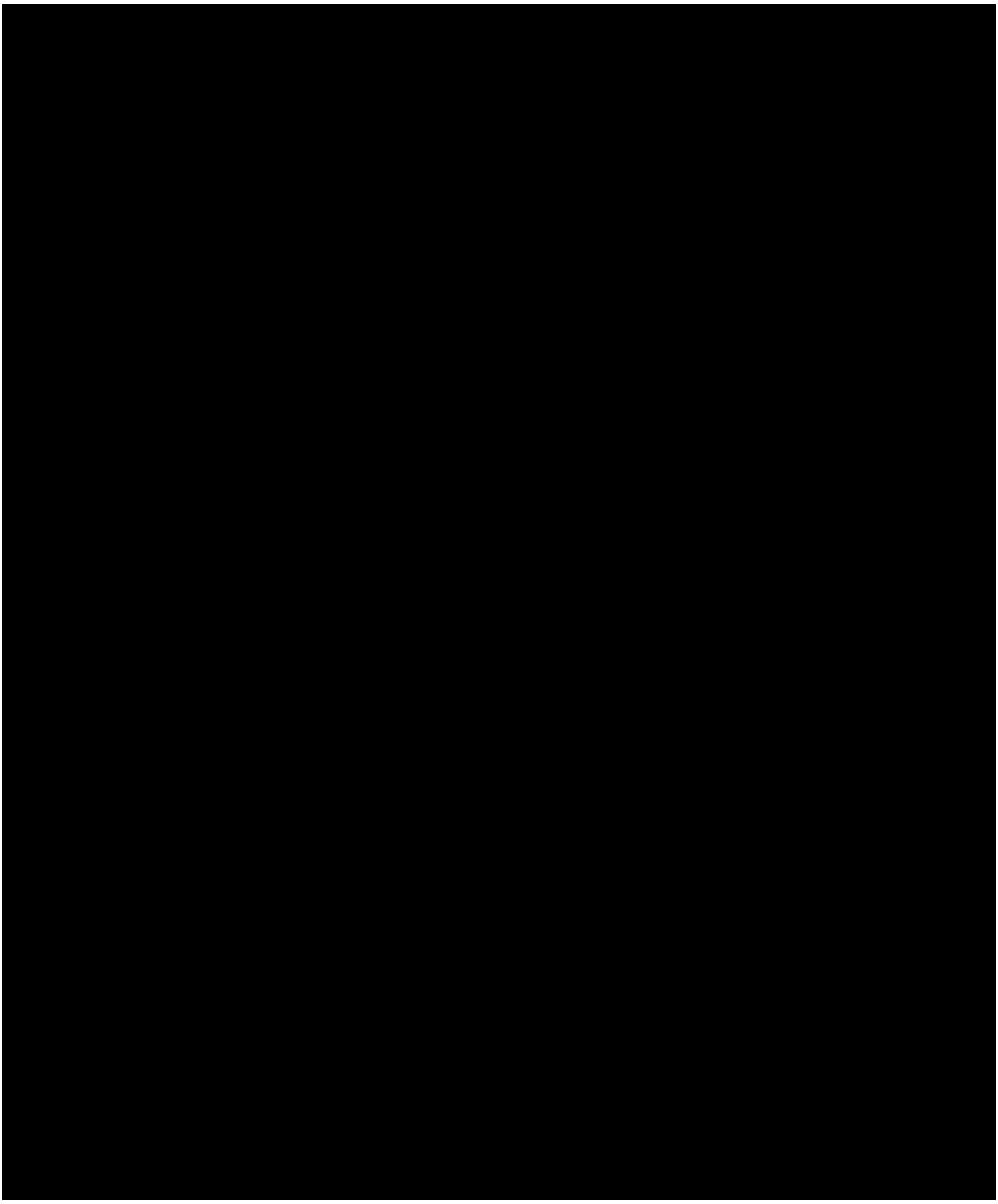
8.7.5 Electrocardiograms

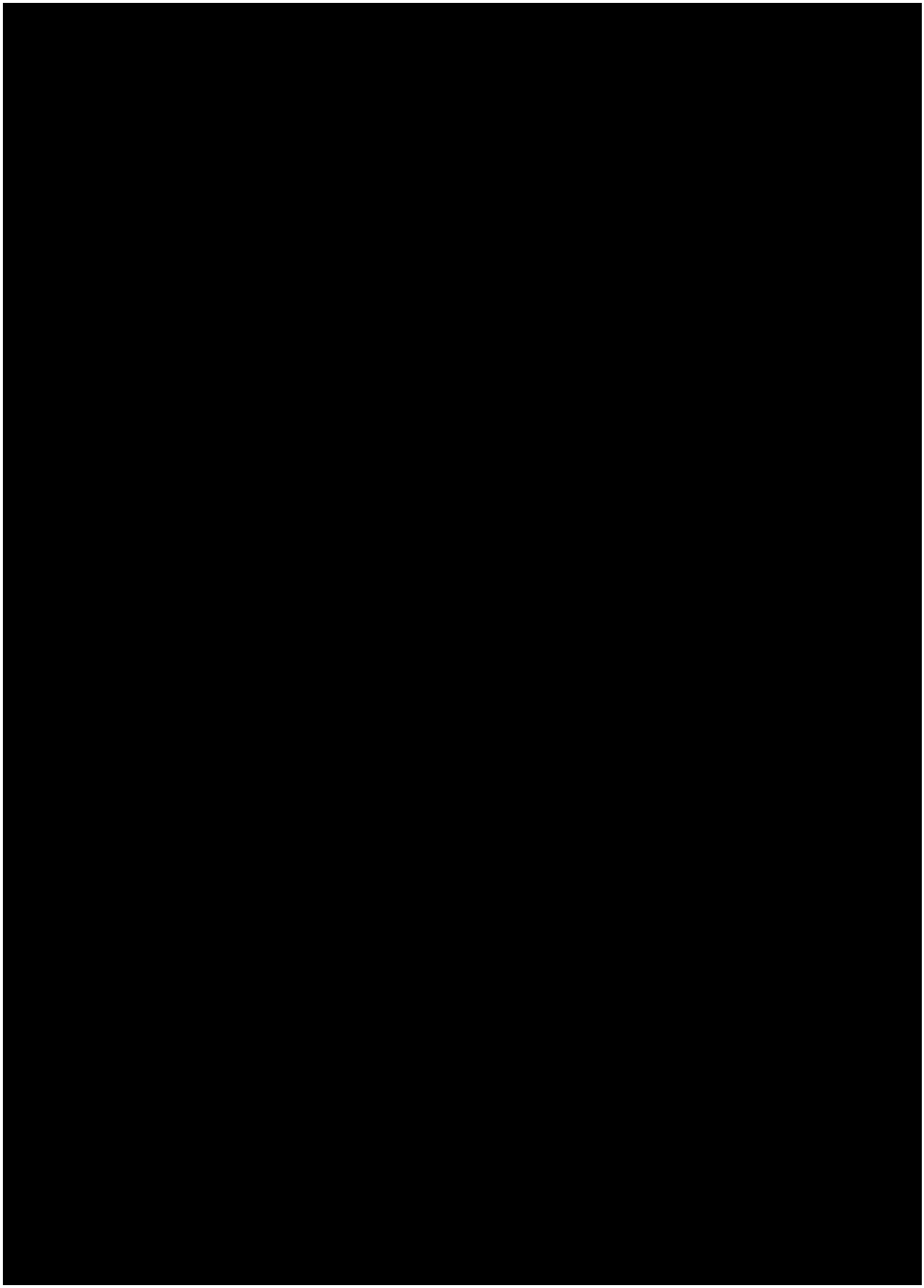
A single 12-lead ECG will be recorded after the subject has been supine for at least 5 minutes.

8.7.6 Renal Biopsy

Renal biopsies performed during the study will be processed and analyzed by a central pathology laboratory. The change from the biopsy results assessed at screening to the (optional) biopsies after 52[redacted] weeks (and/or early discontinuation, if discontinuation occurs after Week 24) of blinded study treatment will be evaluated for LN Class, National Institutes of Health (NIH) Chronicity Index, and NIH Activity Index.[redacted]

[redacted]





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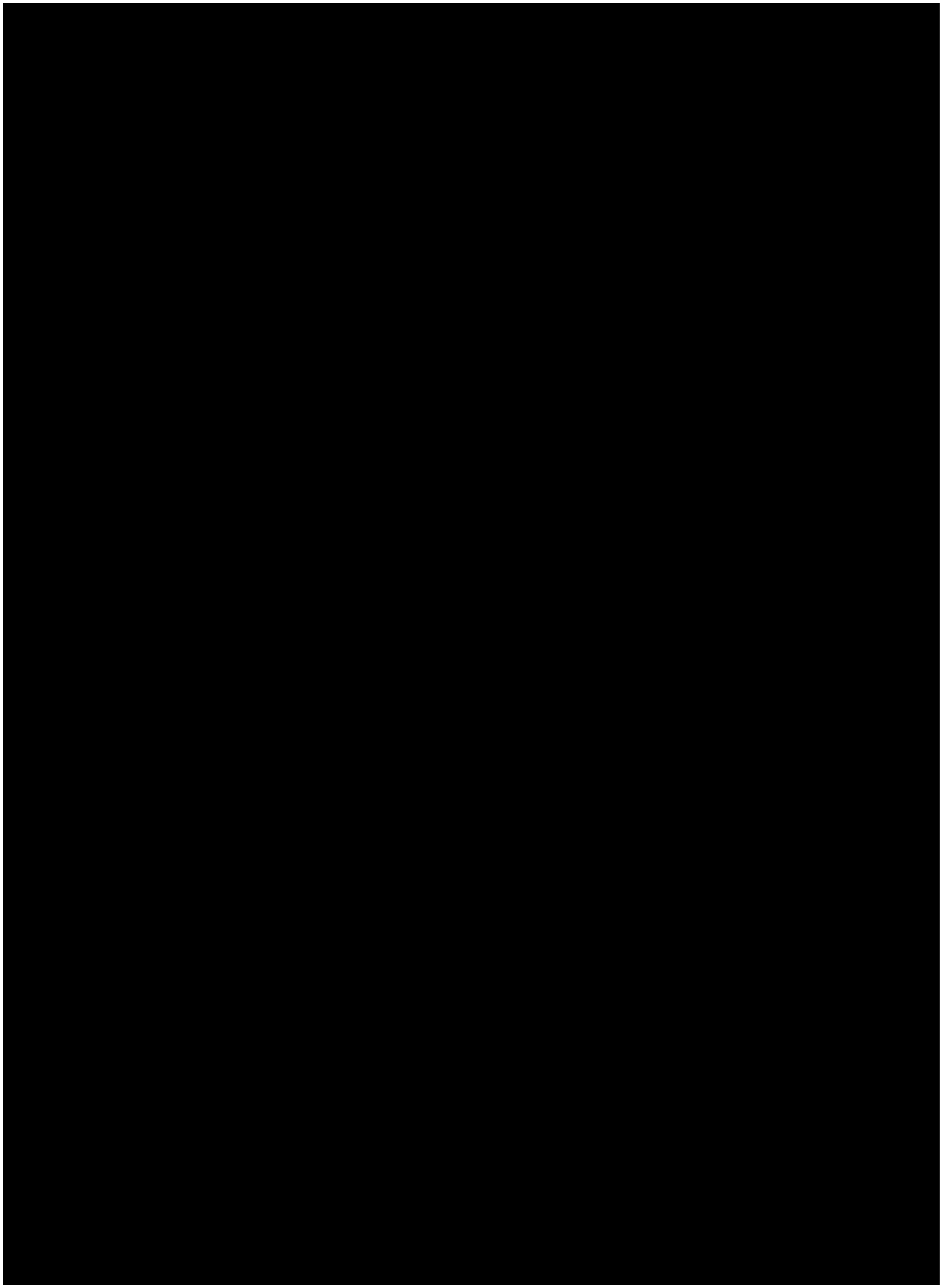


[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

A sample size of 52 randomized subjects in the combined BMS-986165 treatment groups (26 subjects in the BMS-986165 6 mg BID group and 26 in the BMS-986165 3 mg BID group) and 26 subjects in the placebo group will provide 88% power (at a one-sided significance level of 0.10) [redacted]

9.2 Populations for Analyses

The analysis populations are defined as follows:

Population	Description
Full Analysis Set for Part B	All randomized subjects at the beginning of Part B; following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned at randomization at the beginning of Part B
As-treated Set for Part B	All randomized subjects who took at least one dose of blinded study treatment at the beginning of Part B; this population will be used for the safety analyses for Part B. Data in this data set will be analyzed based on randomized treatment for Part B, except in the following cases: • If a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received • If a participant received study treatment from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first treatment received
[redacted]	
MMF	All subjects who take open-label MMF treatment
[redacted]	

9.3 Endpoints

9.3.1 Primary Efficacy Endpoint

Percentage change from baseline in 24-hour UPCR at Week 24

9.3.2 Primary Safety Endpoint

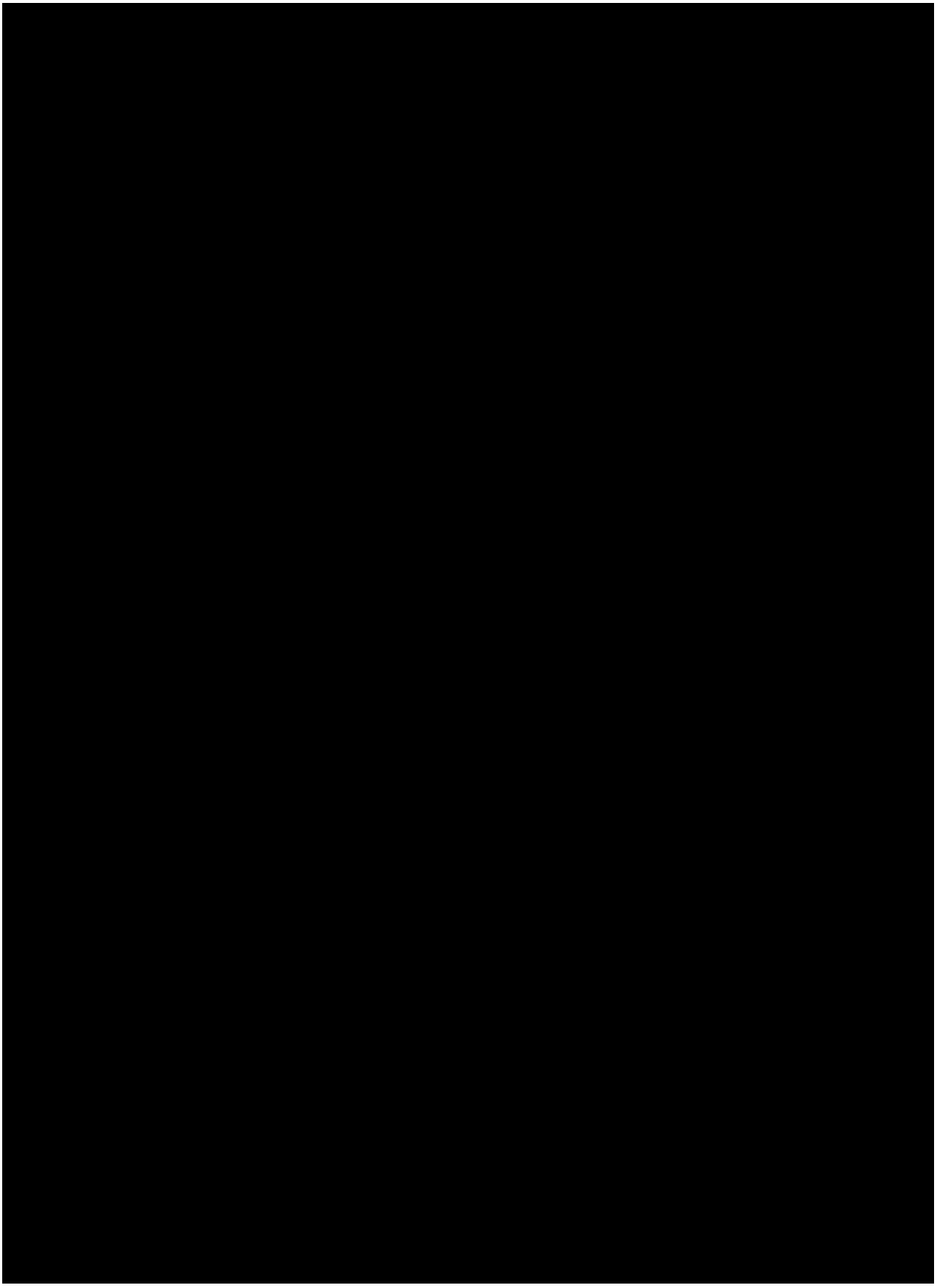
Adverse events, vital signs, ECGs, and laboratory abnormalities from baseline through Week 52

9.3.3 Secondary Efficacy Endpoints

- PRR at Week 24, defined as ≥ 50% reduction from baseline in 24-hour UPCR
- Complete renal response (CRR) at Week 24, defined as both of the following:
  - 24-hour UPCR ≤ 0.5 mg/mg
  - eGFR (using the MDRD equation) ≥ 60 mL/min or ≤ 20% decrease from baseline
- CRR at Week 52
- CRR + successful corticosteroid taper to ≤ 7.5 mg/day at Week 24
- CRR + successful corticosteroid taper to ≤ 7.5 mg/day at Week 52
- PRR at Week 52

[redacted]

[redacted]



[redacted]

9.4 Efficacy Analyses

Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy variables will be summarized for all visits in which the variable is assessed. Complete details of the planned analyses will be documented in the Statistical Analysis Plan (SAP) and finalized before database lock. Summaries will be provided for the Full Analysis Set (FAS) population by randomized treatment for Part B. [redacted]

Additionally, summaries will be provided for the MMF population for subjects continuing open-label treatment.

9.4.1 Primary Endpoint Analysis

The analysis of covariance (ANCOVA) for change from baseline in log-transformed 24-hour UPCR at Week 24 will be performed with treatment groups (BMS-986165 3 mg BID, BMS-986165 6 mg BID, and placebo) and randomization stratification factors (24-hour UPCR < 3.0 mg/mg versus ≥ 3.0 mg/mg, and total cumulative IV corticosteroid methylprednisolone < 250 mg versus ≥ 250 mg) as fixed effects with log-transformed baseline value added into the model as a covariate. Relative treatment differences in percentage change from baseline in 24-hour UPCR at Week 24 on the original scale based on least-square means and the corresponding 2-sided 95% CIs will be provided for combined BMS-986165 treatment groups and placebo. Additionally, least-square means and 2-sided 95% CIs will be provided for the relative difference between each BMS-986165 treatment group and placebo for the FAS.

Prior to unblinding the appropriateness of the log-transformation will be investigated. Further details will be provided in the SAP. For statistical testing, comparison of the combined BMS-986165 treatment group compared to placebo will be performed. There will be no adjustment of the Type 1 error rate for multiple comparisons or testing of multiple endpoints.

9.4.1.1 Imputation Methods for Primary Endpoint

The Multiple Imputation (MI) method will be used for the analysis of primary endpoint at Week 24. The MI is used to impute the missing outcomes for BMS-986165 and placebo treated subjects at Week 24, who discontinued or who have missing values for other reasons at Week 24. The imputation model will have exactly the same baseline covariates as the ANCOVA model above. Multiple draws from the posterior predictive distribution estimates will be used for the imputation; each imputed dataset will be analyzed with ANCOVA model described above. The

PROC MIANALYZE procedure in SAS will be used to pool the ANCOVA results. It should be noted that 24-hour UPCR is collected for the first time postbaseline at Week 24 and not at earlier time points.

The efficacy assessment after the start of protocol-prohibited medication/therapy that could improve LN will be considered missing for the statistical analysis and will be imputed as described above.

9.4.1.2 Sensitivity Analyses for the Primary Endpoint

Additional sensitivity analyses of the primary endpoint may be defined in the SAP.

9.4.1.3 Subgroup Analyses for the Primary Endpoint

Subgroup analyses will be conducted for the primary efficacy endpoint for the FAS using the analysis described in Section 9.4.1 and the imputation methods described in Section 9.4.1.1. Subgroups to be evaluated will include the following:

- Gender
- Age categories at the time of randomization (< 65 years; ≥ 65 years)
- Race
- Baseline 24-hour UPCR (Visit A4) (< 3.0 mg/mg; ≥ 3.0 mg/mg)
- Total cumulative IV corticosteroid (methylprednisolone or parenteral equivalent) dose given in the 16 weeks before randomization (< 250 mg; ≥ 250 mg)

Additional subgroups defined for descriptive summaries will be specified in the SAP.

9.4.2 Secondary [redacted] Efficacy Endpoint Analyses During Week 52 (Part B)

Binary efficacy endpoints (responder/nonresponder) will use stratified Cochran-Mantel-Haenszel (CMH) tests stratified by the factors used for randomization (UPCR < 3.0 mg/mg vs ≥ 3.0 mg/mg) and total cumulative IV corticosteroid (methylprednisolone or parenteral equivalent) dose given in the 16 weeks before randomization (< 250 mg versus ≥ 250 mg) to compare the response rates of BMS-986165 (combined BMS-986165 treatment groups) to placebo for the FAS. Nominal p-values will be provided.

Treatment differences in response rates and the corresponding 2-sided 95% CIs for the difference in proportions between the combined BMS-986165 treatment groups and placebo will be provided. Additionally, treatment differences in response rates and corresponding 95% CIs for the difference in proportions will be provided for each BMS-986165 treatment group compared to placebo. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis.

Continuous efficacy endpoints will be analyzed with an ANCOVA model as specified for the primary endpoint in case the endpoint is only collected at one time point. For continuous efficacy

variables that are more frequently collected, a mixed model for repeated measurement (MMRM) method with structured variance covariance matrix specified for the model will be used.

For statistical testing, comparisons of the combined BMS-986165 treatment group response compared to placebo will be performed for the FAS during 52 weeks. There will be no adjustment of the Type 1 error rate for multiple comparisons or testing of multiple endpoints. Nominal p-values will be provided.

9.4.2.1 Imputation Methods for Secondary [redacted] Endpoints

Nonresponder imputation will be used for the secondary and exploratory binary endpoints, as applicable, for subjects who discontinue early, start a protocol-prohibited medication/therapy that could improve LN, or who have otherwise missing endpoint data at or prior to the specified endpoint.

For continuous secondary [redacted] efficacy endpoints that are only collected at one time point, the MI method as described for the primary endpoints will be applied to deal with missing data.

For continuous secondary [redacted] efficacy endpoints that are collected more frequently, an MMRM method with unstructured variance covariance matrix specified for the model will be used for handling the missing data.

The efficacy assessment after the start of protocol-prohibited medication/therapy that could improve LN will be considered missing for the statistical analysis and will be imputed as described above.

[redacted]

9.5 Safety Analyses

Safety data will be analyzed for treatment-emergent AEs (TEAEs), AEIs, SAEs, laboratory analytes, vital signs, and ECGs. Safety will be summarized using the As-treated population during Week 52 [redacted]. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

9.5.1 Adverse Events

Treatment-emergent AEs, AEIs, SAEs, deaths, AEs leading to discontinuation of IP, AEs by maximum severity, and AEs by relationship to IP will be summarized by the Medical Dictionary for Regulatory Activities system organ class and preferred term by (1) treatment arm in Part B and (2) in LTE period for the following 4 treatment groups separately:

- Group 1: BMS-986165 3 mg BID → BMS-986165 3 mg BID
- Group 2: BMS-986165 6 mg BID → BMS-986165 6 mg BID
- Group 3: Placebo BID → BMS-986165 3 mg BID
- Group 4: Placebo BID → BMS-986165 6 mg BID

AEs for combined BMS-986165 3 mg BID (Group 1 and Group 3) and BMS-986165 6 mg BID (Group 2 and Group 4) may also be summarized as described in the SAP.

All TEAEs, AEIs, as well as any potential adjudicated AE category will also be summarized by preferred term sorted by decreasing frequency.

9.5.2 Vital Signs, Electrocardiograms, and Physical Examinations

Vital signs and ECGs will be summarized as raw, change from baseline, and maximum change from baseline value. Incidence of abnormal ECG and physical examination findings will also be summarized.

9.5.3 Clinical Laboratory Tests

Laboratory analytes will be summarized as raw, change from baseline, and maximum change from baseline value. Incidence of abnormal, high, or low values (based on Common Terminology Criteria for Adverse Events grading for laboratory abnormality) will be summarized. Shift tables will also be provided.

9.6 Other Analyses

9.6.1 Demographics and Baseline Data

Demographics and baseline data will be summarized by treatment for FAS [redacted]. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

9.6.2 Previous and Concomitant Medications

Previous and concomitant medications, categorized by medication group and subgroup according to the World Health Organization Drug Dictionary, will be summarized by (1) treatment arm in Period B [redacted] Medications with an end date prior to the first dose of study treatment will be considered previous medications. The summaries will using the As-treated Set during Week 52 [redacted].

[redacted]

9.6.5 Week 24 Database Lock

A Week 24 database lock will occur once all randomized subjects have completed the Week 24 efficacy assessments or have discontinued prior to Week 24. At this lock, analyses of the collected efficacy and safety results up to Week 24 will be performed in order to aid in planning for subsequent clinical development. Details of these analyses will be described in the SAP.

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APPENDIX 1 ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
aCL	anticardiolipin antibody
ACR	American College of Rheumatology
[redacted]	[redacted]
AE	adverse event
AEI	adverse event of interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
APA	antiphospholipid antibody
APS	antiphospholipid syndrome
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
[redacted]	[redacted]
β2GP1	beta 2-glycoprotein 1
BCRP	breast cancer resistance protein
BID	twice daily
BILAG	British Isles Lupus Assessment Group
BMI	body mass index
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
C	complement
[redacted]	[redacted]
CAPS	catastrophic antiphospholipid syndrome
[redacted]	[redacted]
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CK	creatine kinase
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CRR	complete renal response
CRS	Central Review Services
CT	computed tomography
CTA	Clinical Trial Agreement
[redacted]	[redacted]
CYP450	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee

Abbreviation	Definition
DNA	deoxyribonucleic acid
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	full analysis set
[redacted]	[redacted]
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBc	hepatitis B core
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hpf	high-power field
HR	heart rate
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IGRA	interferon-gamma release assay
IL	interleukin
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
[redacted]	[redacted]
[redacted]	[redacted]
IRT	interactive response technology
ISN/RPS	International Society of Nephrology/Renal Pathology Society
IV	intravenous
JAK	Janus kinase

Abbreviation	Definition
[redacted]	[redacted]
LA	lupus anticoagulant
LD	lactate dehydrogenase
LN	lupus nephritis
LTBI	latent tuberculosis infection
[redacted]	[redacted]
MDRD	Modification of Diet in Renal Disease
MI	multiple imputation
MMF	mycophenolate mofetil
MPA	mycophenolic acid
NIH	National Institutes of Health
[redacted]	[redacted]
[redacted]	[redacted]
NYHA	New York Heart Association
OSS	Ohio SLE Study
[redacted]	[redacted]
[redacted]	[redacted]
PPV	positive predictive value
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRR	partial renal response
QD	once daily
RBC	red blood cell
[redacted]	[redacted]
[redacted]	[redacted]
rSFI	Revised SELENA flare index
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDI	SLICC/ACR Damage Index
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
[redacted]	[redacted]
SLE	systemic lupus erythematosus
[redacted]	[redacted]
SLICC	Systemic Lupus Erythematosus International Collaborating Clinics
Sm	Smith
[redacted]	[redacted]
[redacted]	[redacted]
T4	thyroxine
TB	tuberculosis
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
TID	three times daily
[redacted]	[redacted]
TSH	thyroid-stimulating hormone
TYK	tyrosine kinase
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
US	United States
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Participant' used in the electronic case report form (CRF) is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP)
- as defined by the International Council for Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling information to be provided to subjects and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, global or local) sample informed consent form (ICF) which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the ICF and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The

language must be nontechnical and easily understood.

- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participants' signed ICF and, in the US, the participants' signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

Participants unable to give their written consent (eg, those with stroke or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all

applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/ bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/ accountability, as per the Delegation of Authority Form

Sourced by site, and not supplied by BMS or its vendors (examples include investigational product sourced from the site stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/ accountability, as per the Delegation of Authority Form.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee EDC tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If an electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically

through the BMS EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor, or sourced by the investigator) such as partially used study treatment containers, vials, and syringes may be destroyed on site (as applicable; some sites will return unused study treatments depending on circumstances).

If …	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (eg, study treatments sourced from the site's stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up to date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of nonstudy treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

For sites that will not destroy study treatment on-site, it is the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, provided that

procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

CLINICAL STUDY REPORT AND PUBLICATIONS

A signatory investigator must be selected to sign the clinical study report.

For this protocol, the signatory investigator will be selected as appropriate based on one or more of the following criteria:

- External principal investigator designated at protocol development
- National Coordinating investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing study site or investigator participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Adverse Events

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

Serious Adverse Events

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below) Note: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 8.5.8 for the definition of potential DILI.)

Pregnancy and potential drug-induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 8.5.6 for reporting pregnancies).

Evaluating AEs and SAEs

Assessment of Intensity
The intensity of AEs is determined by a physician and will use the following levels: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. A "reasonable possibility of a relationship" conveys that there are facts, evidences, and/or arguments to suggest a causal relationship rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

Reporting of SAEs to Sponsor or Designee

SAEs, whether related or not related to study drug, and pregnancies must be reported to [redacted] Drug Safety within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: [redacted]

SAE Fax Number:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

SAE Telephone Contact - For questions on SAE/pregnancy reporting, please call:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

The contraception requirements for BMS-986165 include the use of at least one highly effective method of contraception during the study and for 33 days after the last dose (5 half-lives [3 days] plus 30 days [duration of ovulatory cycle]). However, the contraception requirements for

mycophenolate mofetil (MMF) exceed those for BMS-986165, so the MMF requirements will apply to this study.

Per the MMF prescribing information, WOCBP must use effective contraception during treatment and for at least 6 weeks after the final dose of this drug. Subjects must be counseled that MMF may reduce the effectiveness of oral contraceptives, and use of additional barrier methods is required.

For this study, WOCBP must choose either one method from Option 1, or two methods from Option 2 as shown below:

<table>
<tr><th colspan="4">Acceptable Contraception for WOCBP in Study IM011073</th></tr>
<tr><td>Option 1:</td><td colspan="3"></td></tr>
<tr><td>Choose 1</td><td colspan="3">• IUD
• Tubal sterilization
• Patient’s partner vasectomy</td></tr>
<tr><td>Option 2:</td><td>Hormone Methods
(Choose 1)</td><td></td><td>Barrier Methods
(Choose 1)</td></tr>
<tr><td>Choose 1 hormone method
AND
1 barrier method</td><td>Estrogen and Progesterone
• Oral contraceptive
• Transdermal patch
• Vaginal ring

Progesterone only
• Injection
• Implant</td><td>AND</td><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Contraceptive sponge
• Male condom
• Female condom</td></tr>
</table>

IUD = intrauterine device; WOCBP = women of childbearing potential
Note: Although the MMF prescribing information offers a third option (2 barrier methods), this choice is not sufficient for BMS-986165 and is not acceptable for WOCBP in this study.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 90 days after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 90 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 90 days after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 90 days after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.5.6 and APPENDIX 3.

APPENDIX 5 SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria	Immunologic Criteria
1. Acute Cutaneous Lupus*	1. ANA
2. Chronic Cutaneous Lupus*	2. Anti-DNA
3. Oral or nasal ulcers *	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab *
5. Arthritis *	5. Low complement (C3, C4, CH50)
6. Serositis *	6. Direct Coombs' test (do not count in the presence of hemolytic anemia)
7. Renal *	
8. Neurologic *	
9. Hemolytic anemia	
10. Leukopenia *	
11. Thrombocytopenia (<100,000/mm^3)	

Notes:
CLINICAL CRITERIA

(1) <u>Acute Cutaneous Lupus OR Subacute Cutaneous Lupus</u>

- Acute cutaneous lupus: lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash (in the absence of dermatomyositis)
- Subacute cutaneous lupus: nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

(2) <u>Chronic Cutaneous Lupus</u>

Classic discoid rash localized (above the neck) or generalized (above and below the neck), hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap

(3) <u>Oral Ulcers OR Nasal Ulcers</u>

- Oral: palate, buccal, tongue
- Nasal ulcers
- In the absence of other causes, such as vasculitis, Behçet's disease, infection (herpes virus), inflammatory bowel disease, reactive arthritis, and acidic foods

(4) Nonscarring alopecia

Diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia

(5) Synovitis involving 2 or more joints

- Characterized by swelling or effusion
- OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness

(6) Serositis

- Typical pleurisy for more than 1 day OR pleural effusions OR pleural rub
- Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
- In the absence of other causes, such as infection, uremia, and Dressler's pericarditis

(7) Renal

Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein per 24 hours OR red blood cell casts

(8) Neurologic

Seizures, psychosis, mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)

(9) Hemolytic anemia

(10) Leukopenia (< 4000/mm^3) OR Lymphopenia (< 1000/mm^3)

- Leukopenia at least once: In the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension.
- Lymphopenia at least once: in the absence of other known causes such as corticosteroids, drugs, and infection

(11) Thrombocytopenia (< 100,000/mm^3)

At least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

IMMUNOLOGIC CRITERIA

(1) ANA level above laboratory reference range

(2) Anti-dsDNA antibody level above laboratory reference range (or 2-fold the reference range if tested by enzyme-linked immunosorbent assay); indeterminate results are considered positive

(3) Anti-Sm: presence of antibody to Sm nuclear antigen

(4) Antiphospholipid antibody positivity, as determined by

- Positive test for lupus anticoagulant
- False-positive test result for rapid plasma reagin
- Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
- Positive test result for anti–2-glycoprotein I (IgA, IgG, or IgM)

(5) Low complement (C3, C4, or CH50)

(6) Direct Coombs test (in the absence of hemolytic anemia)

Reference:

Petri M, Orbai AM, Alarcon GS, et al. Derivation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012 Aug;64(8):2677-86.

APPENDIX 6 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Dose Equivalence
Prednisone	20 mg
Cortisone	100 mg
Hydrocortisone	80 mg
Deflazacort	26 mg
Prednisolone	20 mg
Methylprednisolone	16 mg
Triamcinolone	16 mg
Budesonide	4 mg
Dexamethasone	3 mg
Betamethasone	2.4 mg

APPENDIX 7 REQUIRED RECOVERY (WASHOUT) TIMES FOR SPECIFIC MEDICATIONS PRIOR TO SCREENING

Medications	Discontinuation Prior to Signing Consent
Abatacept (CTLA4Ig)	12 weeks
Acthar® gel (repository corticotropin injection)	6 weeks
Adalimumab	12 weeks
Alefacept	8 weeks
AMG 623	12 weeks
Anakinra	12 weeks
Apremilast	4 weeks
Atacicept (TACI-Ig)	48 weeks
Azathioprine	4 weeks
Belimumab	12 weeks
BIIB059	15 weeks
Certolizumab pegol	24 weeks
Cyclophosphamide	24 weeks
Cyclosporine	4 weeks for systemic use (oral, IV, etc)
Eculizumab	12 weeks
Efalizumab	8 weeks
Etanercept	4 weeks
Infliximab	12 weeks
Intravenous immunoglobulin	24 weeks
Leflunomide	36 weeks
Lenalidomide with cholestyramine	24 weeks
Lulizumab	6 weeks
Lupuzor (IPP-201101)	12 weeks
Methotrexate	4 weeks
Natalizumab	12 weeks
Obinutuzumab	26 weeks
Ocrelizumab	24 weeks
Ofatumumab	26 weeks
Plasmapheresis	24 weeks
Retinoids (oral isotretinoin and acitretin; topical retinoids are allowed)	4 weeks

Medications	Discontinuation Prior to Signing Consent
Rituximab	52 weeks
Sirolimus	4 weeks
Sulfasalazine	4 weeks
Tabalumab	14 weeks
Tacrolimus	4 weeks for systemic use (oral, IV, etc)
Thalidomide	4 weeks
Tocilizumab	12 weeks
Voclosporin	4 weeks

APPENDIX 8 DIAGNOSTIC CRITERIA FOR SUBSTANCE DEPENDENCE AND ABUSE

The following is from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition:

Diagnostic Criteria for Psychoactive Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

1) Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b) Markedly diminished effect with continued use of the same amount of the substance
2) Withdrawal, as manifested by either of the following:
   a) The characteristic withdrawal syndrome for the substance
   b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3) The substance is often taken in larger amounts or over a longer period than was intended
4) There is a persistent desire or unsuccessful efforts to cut down or control substance use
5) A great deal of time is spent in activities necessary to obtain the substance (eg, visiting multiple doctors or driving long distances), use the substance (eg, chain-smoking), or recover from its effects
6) Important social, occupational, or recreational activities are given up or reduced because of substance use
7) The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (eg, current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.)

Criteria for Severity of Psychoactive Substance Dependence

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate: Symptoms or functional impairment between “mild” and “severe.”

Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

In Partial Remission: During the past 6 months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past 6 months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

A. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by 1 (or more) of the following, occurring at any time in the same 12-month period:

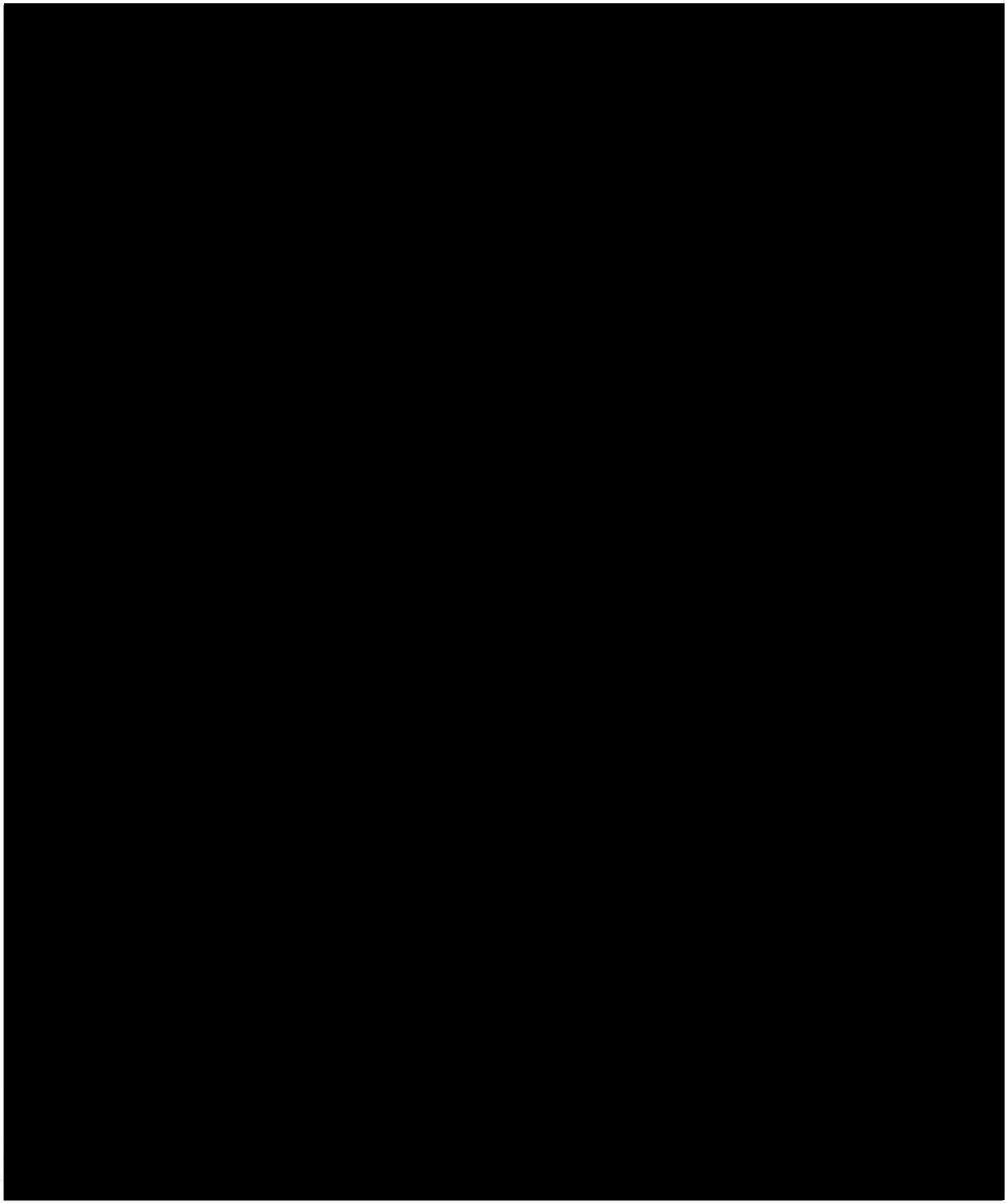
   1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household)

   2) Recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use)

   3) Recurrent substance-related legal problems (eg, arrests for substance-related disorderly conduct)

   4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (eg, arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for substance dependence for this class of substance



APPENDIX 10 SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS/AMERICAN COLLEGE OF RHEUMATOLOGY DAMAGE INDEX

SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS

Patient Name:_____ **Study No.** _____

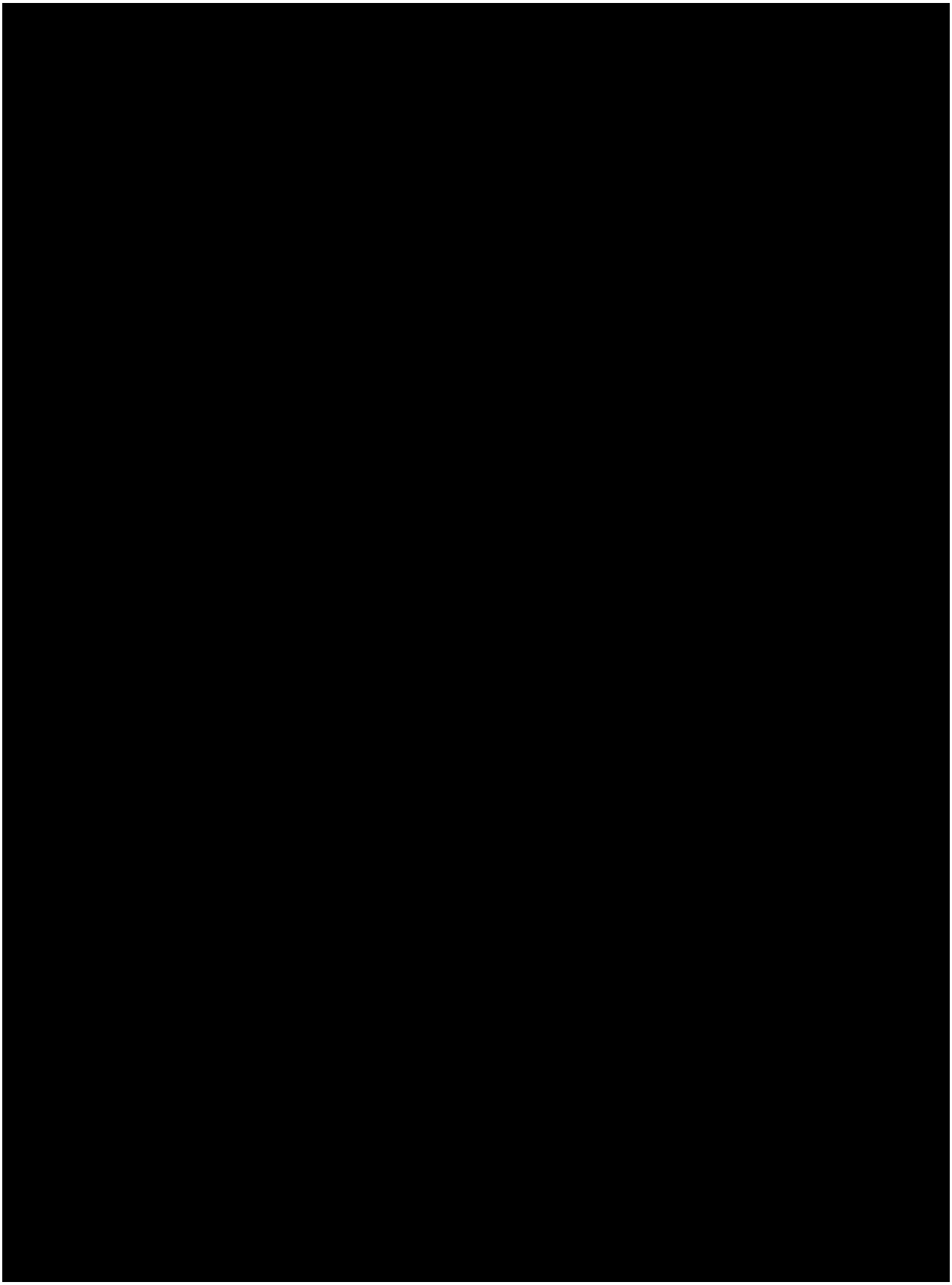
Assessment Date: ___/___/___

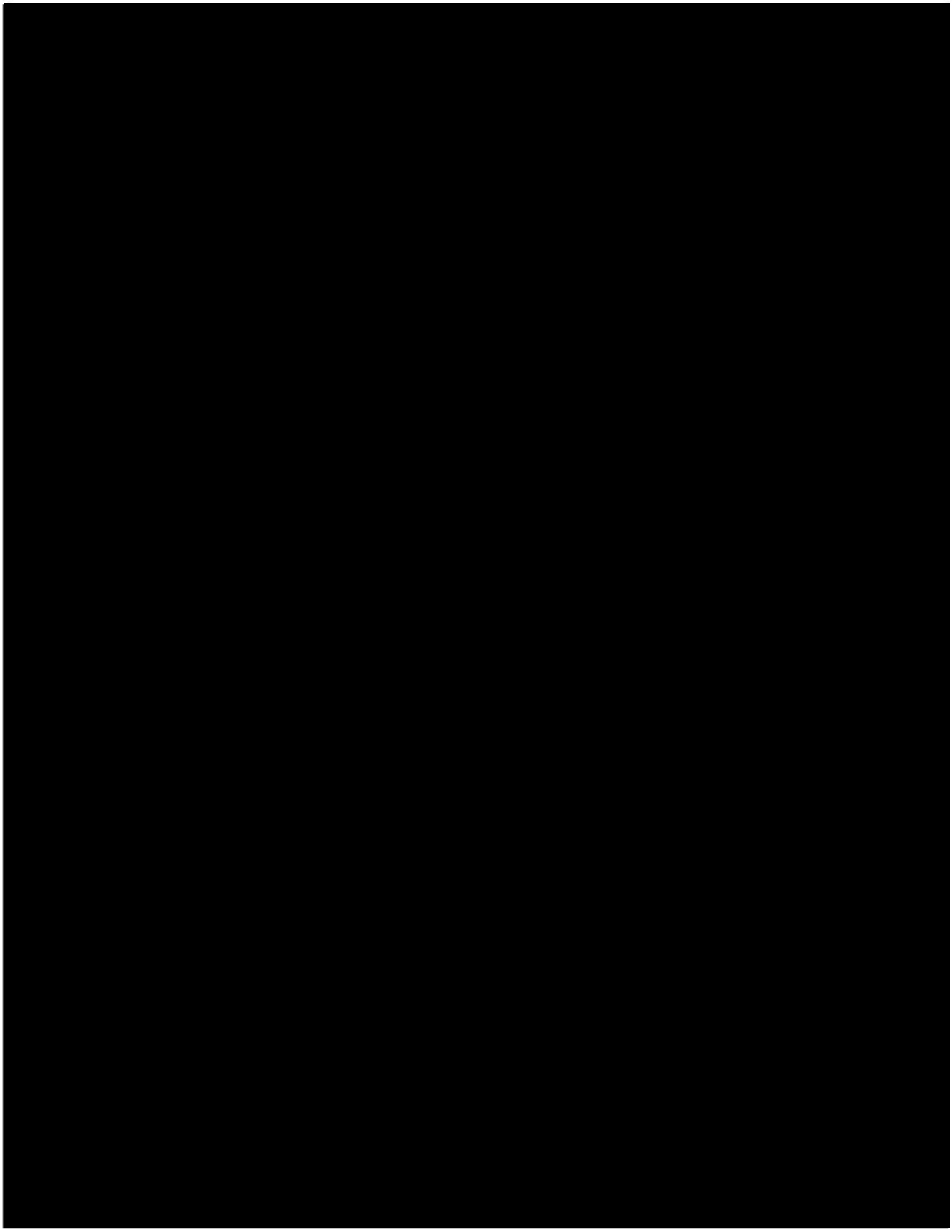
Damage occurring since diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes mean at least 6 months apart to score 2. The same lesion cannot be scored twice.

ITEM	SCORE (circle)
OCULAR (Either eye, by clinical assessment)	
Any cataract ever	0 1
Retinal change OR Optic atrophy	0 1
NEUROPSYCHIATRIC	
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level)	
OR Major psychosis	0 1
Seizures requiring therapy for 6 months	0 1
Cerebral vascular accident ever (Score 2 if >1), resection not for malignancy	0 1 2
Cranial or peripheral neuropathy (excluding optic)	0 1
Transverse myelitis	0 1
RENAL	
Estimated or measured GFR <50%	0 1
Proteinuria 24 h, ≥ 3.5 g	0 1
OR	
End-stage renal disease (regardless of dialysis or transplantation)	3
PULMONARY	
Pulmonary hypertension (right ventricular prominence, or loud P2)	0 1
Pulmonary fibrosis (physical and X-ray)	0 1
Shrinking lung (X-ray)	0 1
Pleural fibrosis (X-ray)	0 1
Pulmonary infarction (X-ray) OR resection not for malignancy	0 1
CARDIOVASCULAR	
Angina OR coronary artery bypass	0 1
Myocardial infarction ever (Score 2 if >1)	0 1 2
Cardiomyopathy (ventricular dysfunction)	0 1
Valvular disease (diastolic murmur, or a systolic murmur > 3/6)	0 1
Pericarditis x 6 months or pericardiectomy	0 1
PERIPHERAL VASCULAR	
Claudication x 6 months	0 1
Minor tissue loss (pulp space)	0 1
Significant tissue loss ever (eg. loss of digit or limb, resection) (Score 2 if >1)	0 1 2
Venous thrombosis with swelling, ulceration, OR venous stasis	0 1
GASTROINTESTINAL	
Infarction or resection of bowel (below duodenum), spleen, liver or gall bladder ever (Score 2 if >1)	0 1 2
Mesenteric insufficiency	0 1
Chronic peritonitis	0 1
Stricture OR upper gastrointestinal tract surgery ever	0 1
Pancreatic insuffiency requiring enzyme replacement or with pseudocyst	0 1
MUSCULOSKELETAL	
Atrophy or weakness	0 1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	0 1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0 1
Avascular necrosis (Score 2 if >1)	0 1 2
Osteomyelitis	0 1
Ruptured tendons	0 1
SKIN	
Alopecia	0 1
Extensive scarring or panniculum other than scalp and pulp space	0 1
Skin ulceration (excluding thrombosis) for more than 6 months	0 1
PREMATURE GONADAL FAILURE	0 1
DIABETES (regardless of treatment)	0 1
MALIGNANCY (Exclude dysplasia)	0 1 2

Reference:

Gladman, DD, Urowitz MB, Goldsmith CH, et al. The Reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in Patients with Systemic Lupus Erythematosus. Arthritis Rheum 1997;40:809-13.





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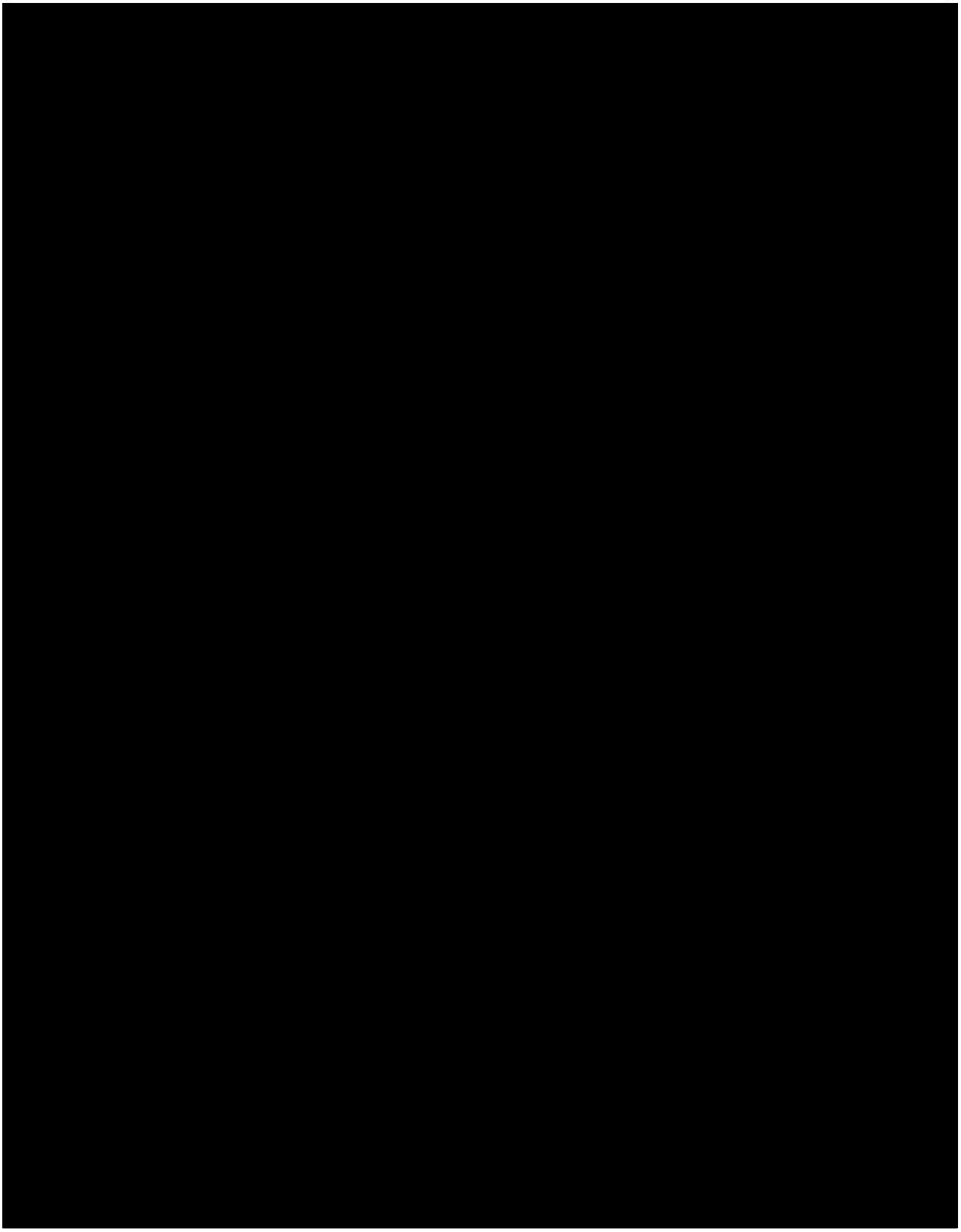
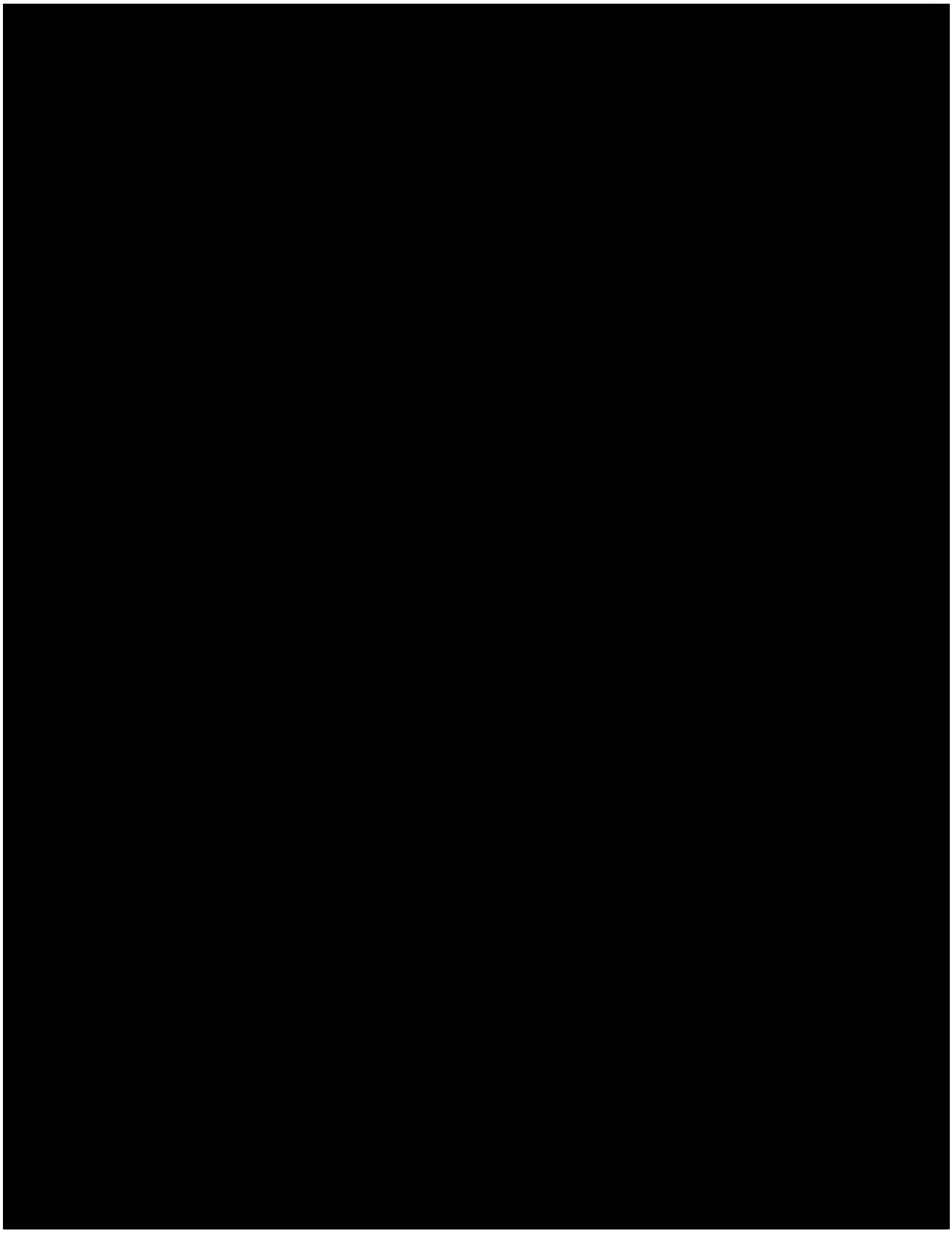




APPENDIX 12 INTERNATIONAL SOCIETY OF NEPHROLOGY/RENAL PATHOLOGY SOCIETY 2003 CLASSIFICATION OF LUPUS NEPHRITIS

ISN/RPS Class	Description of Lupus Nephritis Features
I	Minimal mesangial
II	Mesangial proliferative
III	Focal
	III (A): active lesions: focal proliferative
	III (A/C): active and chronic lesions: focal proliferative and sclerosing
	III (C): chronic inactive lesions with glomerular scars: focal sclerosing
IV	Diffuse
	IV-S: diffuse segmental
	IV-S (A): active lesions: diffuse segmental proliferative
	IV-S (A/C): active and chronic lesions: diffuse segmental proliferative and sclerosing
	IV-S (C): chronic inactive lesions with scars: diffuse segmental sclerosing
	IV-G: diffuse global
	IV-G (A): active lesions: diffuse global proliferative
	IV-G (A/C): active and chronic lesions: diffuse global proliferative and sclerosing
	IV-G (C): chronic inactive lesions with scars: diffuse global sclerosing
V	Membranous
VI	Advanced sclerotic

Reference:

Weening JJ, D'Agati VS, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521-30.

APPENDIX 13 UPDATED CLASSIFICATION CRITERIA FOR ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid antibody syndrome (APS) is present if at least one of the following clinical criteria and one of the laboratory criteria are met[†]:

Clinical Criteria

1. Vascular thrombosis: one or more clinical episodes[‡] of arterial, venous, or small vessel thrombosis[§] in any tissue or organ; thrombosis must be confirmed by objective validated criteria, ie, unequivocal findings of appropriate imaging studies or histopathology (for histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall)
2. Pregnancy morbidity, defined as one of the following:
    a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus
    b) One or more premature births of morphologically normal neonate before the 34th week of gestation because of one of the following:
        i. Eclampsia or severe pre-eclampsia defined according to the standard definitions[26]
        ii. Recognized features of placental insufficiency[**]
    c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory Criteria

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)[27]
2. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, > 40 IgG phospholipid units or IgM phospholipid units, or > 99th percentile) on two or more occasions at least 12 weeks apart, measured by standardized enzyme-linked immunosorbent assay (ELISA)

[†] Classification of APS should be avoided if fewer than 12 weeks or more than 5 years separate the positive antiphospholipid test and the clinical manifestation.

[‡] A thrombotic episode in the past could be considered as a clinical criterion, provided that the thrombosis was proven by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis was found.

[§] Superficial venous thrombosis is not included in the clinical criteria.

[**] Generally accepted features of placental insufficiency include the following:

- Abnormal or nonreassuring fetal surveillance test(s), eg, a nonreactive nonstress test suggestive of fetal hypoxemia
- Abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, eg, absent end-diastolic flow in the umbilical artery
- Oligohydramnios, eg, an amniotic fluid index of 5 cm or less
- A postnatal birth weight less than the 10th percentile for the gestational age

3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer > the 99th percentile), present on two or more occasions at least 12 months apart, measured by standardized ELISA, according to recommended procedures

Reference:

Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295-306.

APPENDIX 14 DIAGNOSIS AND CLASSIFICATION OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

A diagnosis of definite catastrophic antiphospholipid syndrome (CAPS) is made when all of the following 4 criteria are met:

1. Evidence of involvement of 3 or more organs, systems, and/or tissues
    - This usually means clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate
    - Renal involvement is defined by a 50% increase in serum creatinine, severe systemic hypertension (> 180/100 mmHg) and/or proteinuria (> 500 mg/24 hours)
2. Development of manifestations simultaneously or in less than 1 week
3. Confirmation by histopathology of small vessel occlusion in at least 2 organ or tissues
    - Significant evidence of thrombosis must be present, although vasculitis may coexist occasionally
4. Laboratory confirmation of the presence of antiphospholipid antibodies (APAs; lupus anticoagulant and/or anticardiolipin antibodies)
    - If the patient had not previously been diagnosed as having APS, the laboratory confirmation requires that the presence of APAs must be detected on 2 or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite

Note: Probable CAPS may be diagnosed in the following situations:

- Criteria 1, 2, and 4 are met, but not 3
- Criteria 1, 3, and 4 are met; however, a third event occurs between a week and a month later, despite anticoagulation
- Criteria 1 through 4 are met, but only 2 organs/tissues are involved
- Criteria 1 through 4 are met, but APAs could not be assayed 6 weeks apart because the patient died and had never been tested before

References:

Cervera R, Font J, Gomez-Puerta JA, et al. Validation of the primary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 2005;64:1205-9.

Nayer A, Ortega LM. Catastrophic antiphospholipid syndrome: a clinical review. J Nephropathol 2014;3(1):9-17.

APPENDIX 15 MORPHINE MILLIGRAM EQUIVALENTS FOR OPIOIDS

The following table shows daily morphine milligram equivalents for some opioids. This list is not exhaustive, and the 30 mg morphine equivalence limit applies to all opioid analgesics even if they are not listed here.

Opioid	30 mg morphine equivalent
butorphanol	4.3 mg/day
codeine	200 mg/day
dihydrocodeine	120 mg/day
fentanyl transdermal	12.5 mcg/hr
hydrocodone	30 mg/day
hydromorphone	7.5 mg/day
levorphanol tartrate	2.7 mg/day
meperidine HCl	300 mg/day
oxycodone	20 mg/day
oxymorphone	10 mg/day
pentazocine	81.1 mg/day
tapentadol	75 mg/day
tramadol	300 mg/day

Reference:
Centers for Medicare and Medicaid Services. Opioid Oral Morphine Milligram Equivalent Conversion Factors. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf. Accessed August 21, 2018.

APPENDIX 16 OHIO SLE STUDY – CLASSIFICATION OF RENAL FLARE

Flare Severity	Criteria
Mild	Increase in glomerular hematuria from < 5 to > 15 rbcs/hpf, with ≥ 2 acanthocytes/hpf and/or recurrence of ≥ 1 rbc cast, wbc cast (no infection), or both
Moderate	If baseline creatinine < 2 mg/dL, an increase of 0.2 to 1.0 mg/dL
	If baseline creatinine ≥ 2 mg/dL, an increase of 0.4 to 1.5 mg/dL, and/or if baseline UPCR < 0.5, an increase in UPCR to ≥1 mg/mg
	If baseline UPCR = 0.5 to 1 mg/mg, an increase in UPCR to ≥ 2 mg/mg
	If baseline UPCR >1 mg/mg, an increase of ≥ 2-fold with absolute UPCR< 5 mg/mg
Severe	If baseline creatinine < 2 mg/dL, an increase of > 1 mg/dL
	If baseline creatinine ≥ 2 mg/mg, an increase of > 1.5 mg/mg and/or an absolute increase in UPCR > 5 mg/mg

hpf = high-power field; rbc = red blood cell; UPCR = urine protein:creatinine ratio; wbc = white blood cell

Reference:

Rovin BH, Song H, Birmingham DJ, et al. Urine Chemokines as Biomarkers of Human Systemic Lupus Erythematosus Activity. J Am Soc Nephrol 2005;16:467-73.

APPENDIX 17 REVISED SELENA FLARE INDEX

The 2009 revision of the SELENA Flare Index evaluates increases in SLE disease activity within 8 organ systems: mucocutaneous, musculoskeletal, cardiopulmonary, hematological, constitutional, renal, neurological, and gastrointestinal.

Within each organ system, the investigator assesses clinical manifestations and treatment recommendations to arrive at a flare categorization as no flare, mild flare, moderate flare, or severe flare. In this study, investigators will assess only the clinical manifestations; therefore, the treatment component of the rSFI organ systems are not shown here. Also, the renal system will be assessed with the OSS Flare Index, and not with the rSFI.

1. MUCOCUTANEOUS SYSTEM

None	Mild	Moderate	Severe
☐	Clinical: ☐ New/worse/recurrent malar rash New/worse mild oral/nasal ulcers New/worse discoid in a small existing lesion or a very localized area such as ear New mild photosensitive or maculopapular rash New mild alopecia New mild bullous lupus	Clinical: ☐ New/worse extensive oral/nasal ulcers New/worse discoid beyond a very localized area, such as new areas, enlargement, or deepening lesions New/worse moderate photosensitive or maculopapular rash New/worse marked alopecia New/worse small cutaneous ulcers, very limited periungual infarcts New/worse mild to moderate angioedema New/worse moderate bullous lupus New/worse mild to moderate panniculitis	Clinical: ☐ New/worse extensive and/or severe vasculitis, panniculitis, bullous lesions, large cutaneous ulcers, desquamating, necrosis, gangrene, angioedema

2. Musculoskeletal System

None	Mild	Moderate	Severe
☐	Clinical: ☐ New/worse/recurrent polyarthralgias New/mild arthritis of 1 or 2 joints	Clinical: ☐ New/worse/recurrent polyarthritis (3 or more joints)	Clinical: ☐ New/worse/ polyarthritis (3 or more joints) with marked reduction in range of motion or mobility

3. Cardiopulmonary System

None	Mild	Moderate	Severe
☐	Clinical: ☐ New/worse mild pleurisy or pericarditis (symptoms sufficient)	Clinical: ☐ New/worse moderate pleurisy, pericarditis, small pleural effusion (with physical examination findings, radiographs or echo)	Clinical: ☐ New/worse pleural or pericardial effusion requiring tap or window, tamponade New/worse pulmonary hemorrhage, shrinking lung New/worse myocarditis, coronary arteritis

4. Hematological System

None	Mild	Moderate	Severe
☐	Clinical: ☐ Leukopenia - new/worse/recurrent < 3,000 Thrombocytopenia - New/worse/recurrent 50 to 100,000 Hemolytic anemia or anemia of active SLE - HCT > 30	Clinical: ☐ Leukopenia - < 1500 but > 1000 Thrombocytopenia - 30 to 50,000 Hemolytic anemia or anemia of active SLE - HCT < 30, but > 25	Clinical: ☐ Leukopenia - < 1000 Thrombocytopenia - < 30,000 or thrombotic microangiopathy Hemolytic anemia or anemia of active SLE - HCT < 25

Study-specific guidance (Hematologic):

If white blood cell count = 1000, this should be considered MODERATE (< 1500 but ≥ 1000)

If white blood cell count = 1500-3000, this should be considered MILD (Leukopenia-new/worse/recurrent < 3000)

If hematocrit (HCT) is 30-34%, this should be considered MILD (Hemolytic anemia or anemia of active SLE with HCT ≥ 30)

5. Constitutional

None	Mild	Moderate	Severe
☐	Clinical: ☐ Fever New/worse/recurrent up to 101°F (38.3°C) Lymphadenopathy New/worse up to a few small cervical/axillary nodes (< 1cm) Weight loss New weight loss < 5%	Clinical: ☐ Fever New/worse > 101°F (38.3°C) but < 103°F (39.4°C) Lymphadenopathy New/worse lymph nodes outside cervical chain Weight loss 5% to 10% weight loss	Clinical: ☐ Fever New/worse > 103°F (39.4°C) Weight loss > 10% weight loss

Study-specific guidance (Constitutional):

If Fever = 101°F (38.3°C), this should be considered MILD. If Fever ≥ 103°F (39.4°C), this should be considered SEVERE.

6. Renal System

None	Mild	Moderate	Severe
☐	Clinical: ☐ New/worse protein/cr > 0.2 but < 0.5	Clinical: ☐ New/worse urine pr/cr > 0.5 but < 1.0 Increase in RBC/hpf from < 5 to > 15 with > 2 acanthocytes/hpf	Clinical: ☐ Urine pr/cr > 1.0 if baseline < 0.3 Urine pr/cr doubled if baseline is Urine pr/cr > 5.0 New RBC casts or mixed RBC casts Biopsy with new/worse aggressive lesions (necrosis, crescents) Biopsy with Class IV Rapidly progressive glomerulonephritis Decreased GFR in last 3 months If baseline Cr < 2, increase of > 0.2 mg/dl If baseline Cr > 2, increase of > 0.4 mg/dl

7. Neurological System

None	Mild	Moderate	Severe
☐	Clinical: ☐ Minimal/intermittent ACR neuropsychiatric SLE syndrome	Clinical: ☐ New/worsening persistent ACR neuropsychiatric SLE syndrome	Clinical: ☐ Acute delirium or confusional state (organic brain syndrome) Coma Status epilepticus Cranial nerve palsy (including optic) Stroke due to CNS vasculitis Aseptic meningitis Mononeuritis multiplex Longitudinal myelitis Chorea Cerebellar ataxia Myositis with weakness

8. Gastrointestinal System

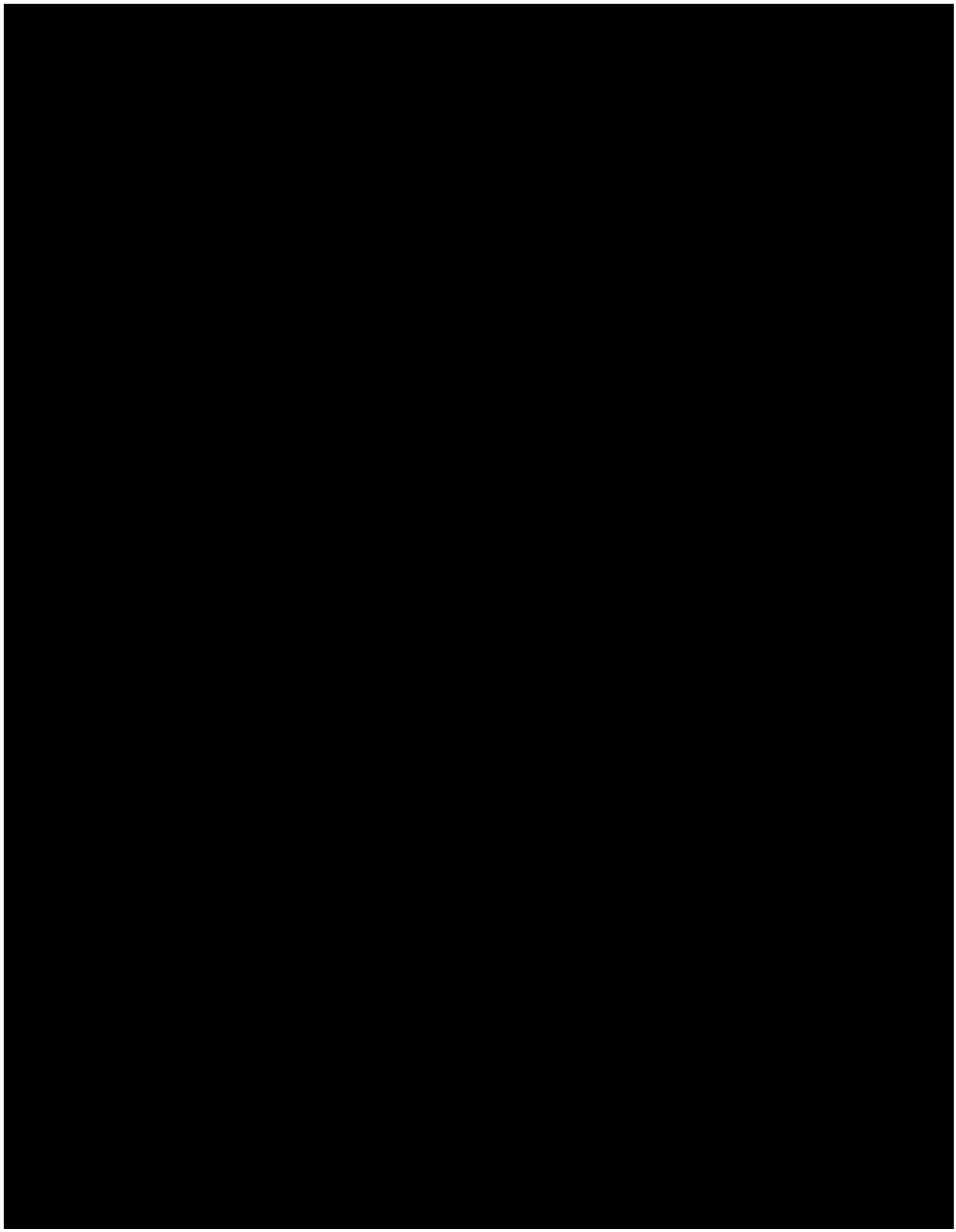
None	Mild	Moderate	Severe
☐	Clinical: ☐ New/worse LFTs > 2x normal but < 4x normal	Clinical: ☐ New/worse LFT's > 4x normal New/worse pancreatitis with increased amylase, but no IV therapy New/worse clinical peritonitis with no ascites	Clinical: ☐ New/worse lupus peritonitis with ascites New/worse enteritis, colitis or protein-losing enteropathy New/worse intestinal pseudo-obstruction with hypomotility New/worse pancreatitis requiring IV therapy New/worse GI vasculitis (mesenteric or other GI organ)

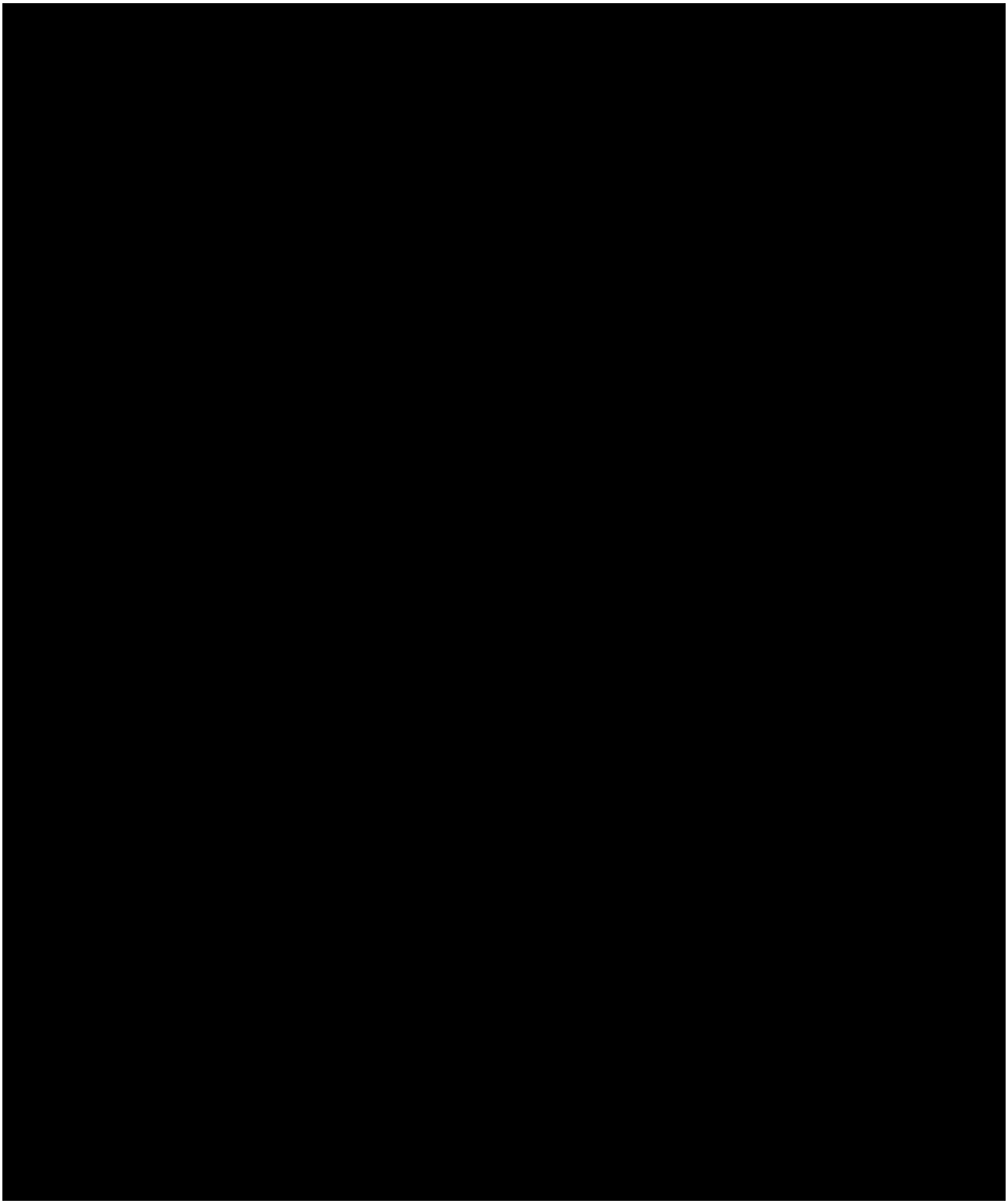
Study-specific guidance (Gastrointestinal):

If new or worse liver function tests (LFTs) are 4 times the upper limit of normal, this should be considered MODERATE (New/worse LFTs ≥ 4 × normal)

Reference:

Isenberg D, Sturgess J, Allen E, et al. Study of Flare Assessment in Systemic Lupus Erythematosus Based on Paper Patients. Arthritis Care Res (Hoboken) 2018;70(1):98-103.





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APPENDIX 20 TUBERCULOSIS RISK ASSESSMENT TOOL

A subject with any of the 3 following high-risk factors will have an interferon-gamma release assay (IGRA):

	Yes	No
1. Recent close or prolonged contact with someone with infectious TB disease		
2. High-risk profession or situations, like being patient-facing, eg, healthcare providers		
3. Recent travel to or from a high burden country for TB (please see country list from UN partner website, Stop TB): http://www.stoptb.org/countries/tbdata.asp		

TB = tuberculosis; UN = United Nations